Vaccine 37 (2019) 5877–5885

Contents lists available at ScienceDirect

Vaccine

journal homepage: www.elsevier.com/locate/vaccine

The adjuvanted recombinant zoster vaccine co-administered with a tetanus, diphtheria and pertussis vaccine in adults aged ≥50 years: A randomized trial

Ana Strezova [a], Himal Lal [b,1], Igwebuike Enweonye [c], Laura Campora [a], Pierre Beukelaers [a], Nathan Segall [d], Thomas C. Heineman [b,2], Anne E. Schuind [e,*], Lidia Oostvogels [a,3]

[a] GSK, 20 Avenue Fleming, 1300 Wavre, Belgium
[b] GSK, 2301 Renaissance Blvd, King of Prussia, PA 19406-2772, USA
[c] GSK, 81-87 Hullenberweg, Amsterdam 1101 CL, Netherlands
[d] Clinical Research Atlanta, 175 Country Club Dr. Ste A, Stockbridge 30281, GA, USA
[e] GSK, 14200 Shady Grove Road, Rockville, MD 20850, USA

ARTICLE INFO

Article history:
Received 3 April 2019
Received in revised form 30 July 2019
Accepted 1 August 2019
Available online 20 August 2019

Keywords:
Herpes zoster
Adjuvanted recombinant zoster vaccine
Reduced-antigen-content diphtheria-tetanus-acellular pertussis vaccine
Co-administration
Immune response
Safety

ABSTRACT

Background: This study evaluated immunogenicity and safety of the adjuvanted recombinant zoster vaccine (RZV) and the reduced-antigen-content diphtheria-tetanus-acellular pertussis vaccine (Tdap) when co-administered in adults aged ≥50 years.

Methods: In this open label, multi-center study (NCT02052596), participants were randomized 1:1 to the Co-Administration group (RZV dose 1 and Tdap at Day 0 [D0], RZV dose 2 at Month 2 [M2]) or Control group (Tdap at D0, RZV dose 1 at M2, RZV dose 2 at M4). Co-primary objectives were evaluation of the vaccine response rate (VRR) to RZV in the Co-Administration group, and demonstration of non-inferiority of the humoral responses to RZV and Tdap in the Co-Administration compared to Control group. Reactogenicity and safety of RZV and Tdap were also assessed.

Results: VRR to RZV was 97.8% in the Co-Administration group. The non-inferiority criterion was met for the humoral response to RZV and for 4 Tdap antigens, but was not met for the Tdap antigen pertactin. Occurrences of solicited, unsolicited and serious adverse events, and potential immune-mediated diseases were similar between groups.

Conclusions: Co-administration of RZV and Tdap did not interfere with the humoral immune response to RZV or 4 of the 5 Tdap antigens. No safety concerns were identified.

1. Introduction

Primary infection with varicella-zoster virus (VZV) causes chickenpox; thereafter VZV establishes latency in sensory ganglia. Reactivation of latent VZV results in herpes zoster (HZ), which typically manifests as a painful, dermatomal rash [1–3]. Complications of HZ include postherpetic neuralgia, ophthalmic disease, myelitis, and encephalitis [1,4]. The risk of HZ increases with age, with more than 60% of all HZ cases occurring after 50 years of age (YOA) [5,6]. This increase in HZ risk is thought to be caused by an age-related decline in VZV-specific cellular immunity [7–10].

An adjuvanted recombinant zoster vaccine containing the VZV glycoprotein E (gE) and the $AS01_B$ Adjuvant System (Shingrix, referred to as RZV hereafter [11]) demonstrated 97.2% and 91.3% overall efficacy against HZ in adults aged ≥50 and ≥70 YOA, respectively [12,13]. Furthermore, RZV induced robust humoral

Abbreviations: CI, confidence interval; D, day; DT, diphtheria toxoid; ELISA, enzyme-linked immunosorbent assay; FHA, filamentous hemagglutinin; gE, varicella-zoster virus glycoprotein E; GM(C), geometric mean (concentration); HZ, herpes zoster; IIV4, inactivated quadrivalent influenza vaccine; IU, international units; LL, lower limit; M, month; pIMDs, potential immune-mediated diseases; PPSV23, 23-valent pneumococcal polysaccharide vaccine; PRN, pertactin; PT, pertussis toxoid; RZV, recombinant zoster vaccine; (S)AE, (serious) adverse event; SD, standard deviation; Tdap, adult formulations of vaccines containing tetanus and diphtheria toxoids and acellular pertussis antigens; TT, tetanus toxoid; UL, upper limit; VRR, vaccine response rate; VZV, varicella-zoster virus; YOA, years of age.

* Corresponding author.
E-mail addresses: ana.x.strezova@gsk.com (A. Strezova), himallal@pfizer.com (H. Lal), igwebuike.x.enweonye@gsk.com (I. Enweonye), laura.e.campora@gsk.com (L. Campora), pierre.x.beukelaers@gsk.com (P. Beukelaers), nsegall@clinicalresearchatlanta.com (N. Segall), tch3768@gmail.com (T.C. Heineman), Anne.E.Schuind@gsk.com (A.E. Schuind), cornelia.oostvogels@orange.fr (L. Oostvogels).
[1] Current address: Pfizer Inc., 500 Arcola Rd, Collegeville, PA 19426, USA.
[2] Current address: Halozyme Therapeutics, 11388 Sorrento Valley Road, San Diego, CA 92121, USA.
[3] Current address: CureVac AG, Paul-Ehrlich-Straße 15, Tübingen 72076, Germany.

https://doi.org/10.1016/j.vaccine.2019.08.001
0264-410X/

and cellular immune responses in all age groups [14]. RZV is currently approved in several countries worldwide for prevention of HZ in adults aged ≥50 YOA [15–17]. In the US, RZV is recommended for the prevention of HZ and related complications for immunocompetent adults ≥50 YOA, including those who previously received the live zoster vaccine [18].

Older adults are also at increased risk for other infections and their complications, such as influenza, pneumococcal disease, pertussis, diphtheria and tetanus [19–24]. Adult formulations of vaccines containing tetanus and diphtheria toxoids and acellular pertussis antigens (Tdap) have been developed to prevent pertussis and to re-establish protection against diphtheria and tetanus [25]. Vaccination of adults is important to prevent outbreaks of these vaccine-preventable diseases and to help prevent pertussis transmission to infants younger than 12 months of age [26,27]. For these reasons, vaccination against diphtheria, tetanus, and pertussis is currently recommended for adults in many countries [26]. In the US, the Centers for Disease Control and Prevention recommend a single dose of Tdap for adults ≥19 YOA previously not vaccinated with Tdap [28].

Recent trials indicate that the immunogenicity of RZV is preserved and that the reactogenicity of neither of the vaccines is significantly impacted when the first dose is co-administered with either a seasonal inactivated quadrivalent influenza vaccine (IIV4) or a 23-valent pneumococcal polysaccharide vaccine (PPSV23) [29,30]. Given that administration of vaccines at a single visit is more convenient and cost effective, and might improve vaccine coverage, this study evaluated the immunogenicity and safety when the first dose of RZV was co-administered with Tdap as compared to sequential administration.

2. Methods

2.1. Study design

This phase III, open-label, randomized, multi-center study was conducted at 13 study centers in the US between February 2014 and April 2016. Participants were randomized 1:1 to one of two parallel study arms using a central randomization system on the internet (SBIR, GSK). Participants in the Co-Administration (Co-Ad) group received the first dose of RZV and Tdap co-administered at Day 0 (D0), and the second dose of RZV at Month 2 (M2). Participants in the Control group received Tdap at D0, the first dose of RZV at M2 and the second dose of RZV at M4.

The study documents were reviewed and approved by applicable regulatory agencies and ethics committees. The study was conducted in accordance with the Declaration of Helsinki and the principles of Good Clinical Practice and is registered on ClinicalTrials.gov (NCT02052596). Full clinical study documents including protocol and clinical study report are available at http://www.gsk-clinicalstudyregister.com (study 116887). Anonymized individual participant data and study documents can be requested for further research at www.clinicalstudydatarequest.com.

Co-primary objectives of the study were (*1*) to evaluate the vaccine response rate (VRR) to RZV (based on humoral immune response) in the Co-Ad group 1M post-RZV dose 2; (*2*) to demonstrate non-inferiority of the humoral immune response to two doses of RZV in the Co-Ad versus Control group 1M post-RZV dose 2; and (*3*) to demonstrate non-inferiority of humoral responses to Tdap in the Co-Ad versus Control group 1M post-Tdap vaccination. The secondary objective of this study was to evaluate the safety and reactogenicity of RZV and Tdap when co-administered or administered sequentially.

2.2. Study participants

Adults were eligible for participation in the study if they were ≥50 YOA at the time of first vaccination, provided written informed consent before study start, and, in the opinion of the investigator, were able to comply with the requirements of the protocol. Adults were excluded from participation if they had a history of HZ, or had received any HZ, VZV, or Tdap vaccine at any time before the study or any vaccine against diphtheria or tetanus within the 5 years preceding the study. Persons on chronic immunosuppressive therapy were also excluded from participation. Detailed inclusion/exclusion criteria are presented in Supplementary Text 1.

2.3. Study vaccines

Both vaccines were administered intramuscularly in the deltoid muscle of the upper arm (non-dominant arm for RZV, dominant arm for Tdap). The RZV vaccine (Shingrix, GSK) contains 50 μg of VZV gE antigen and the GSK proprietary $AS01_B$ Adjuvant System (containing 50 μg MPL [3-*O*-desacyl-4′-monophosphoryl lipid A; produced by GSK], 50 μg QS-21 [*Quillaja saponaria* Molina, fraction 21; licensed by GSK from Antigenics LLC, a wholly owned subsidiary of Agenus Inc., a Delaware, USA corporation] and liposome) per 0.5 mL of reconstituted vaccine. The Tdap vaccine (Boostrix, GSK) contains ≥2 international units (IU) diphtheria toxoid (DT), ≥20 IU tetanus toxoid (TT), ≥8 μg pertussis toxoid (PT), 8 μg filamentous hemagglutinin (FHA) and 2.5 μg pertactin (PRN) per 0.5 mL prefilled monodose syringe. Tdap antigens are adjuvanted with aluminum salts.

2.4. Outcomes and assessments

2.4.1. Assessment of immunogenicity

Humoral immune responses to the study vaccines were assessed from blood samples (~8 mL) collected from participants in the Co-Ad group at D0 (pre-vaccination for RZV and Tdap), M1 (1M post-Tdap vaccination), and M3 (1M post-RZV dose 2); and in the Control group at D0 (pre-Tdap vaccination), M1 (1M post-Tdap vaccination), M2 (pre-RZV vaccination), and M5 (1M post-RZV dose 2). Anti-gE antibody concentrations were measured using an anti-gE enzyme-linked immunosorbent assay (ELISA) with a seropositivity cut-off of 97 milli IU (mIU)/mL. VRR was defined as the percentage of participants who had at least: (i) a 4-fold increase in the post-RZV dose 2 anti-gE antibody concentration compared to the anti-gE cut-off for participants who were seronegative at baseline, or (ii) a 4-fold increase in the post-RZV dose 2 anti-gE antibody concentration compared to the pre-RZV vaccination anti-gE concentration for participants who were seropositive at baseline.

Antibodies against DT (anti-D), TT (anti-T) and the three pertussis antigens (anti-PT, anti-FHA and anti-PRN) were measured by ELISA, with seropositivity cut-offs of 0.057, 0.043, 2.693, 2.046, and 2.187 IU/mL, respectively.

2.4.2. Assessment of reactogenicity and safety

Diary cards were provided to the participants to record solicited and unsolicited adverse events (AEs). Solicited local (injection site pain, redness and swelling) and general (fatigue, fever, gastrointestinal symptoms, headache, myalgia, and shivering) AEs were recorded for 7 days (D0–D6) after each vaccination. Unsolicited AEs were recorded for 30 days (D0–D29) after each vaccination. All solicited AEs were graded on a scale from 0 (characterized by a surface diameter <20 mm [for swelling and redness], oral temperature <37.5 °C [for fever] or absent [for all other solicited AEs]) to 3 (characterized by a surface diameter >100 mm

[for redness and swelling], significant at rest and preventing normal everyday activities [for pain], oral temperature >39.0 °C [for fever] or preventing normal activity [for all other solicited AEs]). Unsolicited AEs were graded by the investigators on a scale from 1 (mild: causing minimal discomfort and not interfering with everyday activities) to 3 (severe: preventing normal everyday activities). All solicited local reactions were considered causally related to vaccination. Causal relationship to vaccination of all other AEs was assessed by the investigators.

Serious AEs (SAEs) and potential immune-mediated diseases (pIMDs) were recorded from administration of the first study vaccine dose until the end of the study (approximately 12M post-RZV dose 2 in each group).

Suspected HZ, defined as appearance of a new rash characteristic of HZ and diagnosed by the investigator, were collected until study end. HZ and/or HZ complications constituted an AE or SAE, as appropriate.

2.5. Statistical analyses

For binomial outcomes, the exact 2-sided 95% confidence intervals (CIs) for proportions within groups were calculated using the Clopper-Pearson method [31], while the 2-sided standardized asymptotic 95% CIs for the between group differences were calculated using Miettinen and Nurminen method [32].

An Analysis of Covariance model was used to analyze post-vaccination log-transformed concentrations of anti-gE, anti-FHA, anti-PT and anti-PRN antibodies. The fixed-effect model for anti-gE included the treatment and age strata as fixed effects. For anti-FHA, anti-PT and anti-PRN, the fixed-effect model included only treatment as a fixed effect. The pre-vaccination log-transformed concentrations were included as continuous covariates in both models. Geometric means (GMs) of post-vaccination concentrations were calculated conditionally to the means of the pre-vaccination log-transformed concentrations.

The 2-sided 95% CIs for the mean of log-transformed concentrations were first obtained assuming that log-transformed values were normally distributed with unknown variance. The 2-sided 95% CIs for the GMs were then obtained by exponential transformation of the CIs for the mean of log-transformed concentrations.

Missing data or non-evaluable measurements were treated as missing completely at random processes. No adjustment was made for the type I error due to multiplicity as the null hypotheses must simultaneously show a significant beneficial effect for the study main objective to be met.

The analysis of immunogenicity was performed on the according-to-protocol (ATP) cohort for immunogenicity which included participants who met all eligibility criteria, complied with the study procedures and intervals allowed for the analysis, and for whom data concerning immunogenicity endpoint measures were available. Descriptive analyses of reactogenicity and safety were performed on the total vaccinated cohort (TVC) and included all participants with at least 1 documented administered vaccine dose, except those from a study center that was excluded from the analysis.

All statistical analyses were performed using the Statistical Analysis Systems Drug Development Version 4.3.3.

2.5.1. Co-primary objectives

The first co-primary objective was met if the lower limit (LL) of the 2-sided 95% CI of the VRR for anti-gE antibody concentrations in the Co-Ad group was ≥60%.

The second co-primary objective was demonstrated if, 1M post-RZV dose 2, the upper limit (UL) of the 2-sided 95% CI of the adjusted geometric mean concentration (GMC) ratio (Control over Co-Ad) was <1.5.

The third co-primary objective, non-inferiority of the humoral immune response to Tdap in the Co-Ad compared to the Control group, was demonstrated if, 1M post-Tdap vaccination, the UL of the 2-sided 95% CI of the adjusted GMC ratio (Control over Co-Ad) was <1.5 for anti-FHA, anti-PT, and anti-PRN; and the UL of the 2-sided 95% CI for the difference in percentage of participants (Control minus Co-Ad) with antibody concentrations ≥1.0 IU/mL for anti-D and anti-T was <10%.

2.5.2. Secondary objective

Reactogenicity and safety of both study vaccines were assessed using descriptive statistics.

2.5.3. Sample size calculation

To demonstrate all co-primary objectives with a global power of 90%, a sample size of 778 evaluable participants (389 per study group) were needed. Assuming 5% non-evaluable participants, 820 participants (410 per study group) were needed to be enrolled.

3. Results

3.1. Study participants

From 904 enrolled participants, 903 were randomized and received at least one study vaccine dose. Of these, 830 (412 Co-Ad, 418 Control) were included in the TVC. Seventy-three vaccinated participants were excluded from all analyses as their study center was closed in August 2014. To maintain the statistical power, 76 additional participants were subsequently enrolled in this study, who were counted in the total of 904 enrollees. Of the 830 vaccinated participants, 771 (377 Co-Ad, 394 Control) were included in the ATP cohort for immunogenicity and 768 (385 Co-Ad, 383 Control) of the 830 vaccinated participants completed the study up to the last contact for safety (M14 in Co-Ad, M16 in Control) (Fig. 1). In the TVC, demographic characteristics were well-balanced between study groups (Table 1). The mean ages were 63.4 (standard deviation [SD]: 8.4) and 63.1 (SD: 9.0) years in the Co-Ad and Control groups, respectively, and most participants were Caucasian in both study groups. The gender distribution was similar between the two study groups.

3.2. Immunogenicity

One month post-RZV dose 2, VRR to RZV was 97.8% (95% CI: 95.8–99.1) in the Co-Ad group; therefore, the success criterion for the VRR objective (LL of the 95% CI ≥60%) was met (Table 2).

The adjusted GMC ratio (Control over Co-Ad) for anti-gE antibodies 1M post-RZV dose 2 was 1.11 (95% CI: 1.02–1.21); therefore, the non-inferiority criterion (UL of the 95% CI <1.5) for the humoral immune response to RZV in the Co-Ad versus the Control group was met (Table 2).

The non-inferiority criterion (UL of 95% CI <1.5) for the humoral immune response to Tdap in the Co-Ad compared to the Control group was met for the pertussis antigens except PRN. The adjusted GMC ratios (Control over Co-Ad) for anti-FHA, anti-PT, and anti-PRN antibodies 1M post-Tdap vaccination were 1.24 (95% CI: 1.07–1.44), 1.17 (95% CI: 1.00–1.36), and 1.27 (95% CI: 1.02–1.58), respectively. The anti-PRN GMC increased more than 12-fold over pre-vaccination in the Co-Ad group, and post-vaccination anti-PRN seropositivity rates were similar between the Co-Ad and Control groups 1M post-Tdap vaccination (Table 3).

The difference in percentage of participants (Control minus Co-Ad) with antibody concentrations ≥1.0 IU/mL 1M post-Tdap vaccination were 1.52% (95% CI: −4.66–7.72) and −0.84% (95% CI: −3.73–2.02) for anti-D and anti-T, respectively.

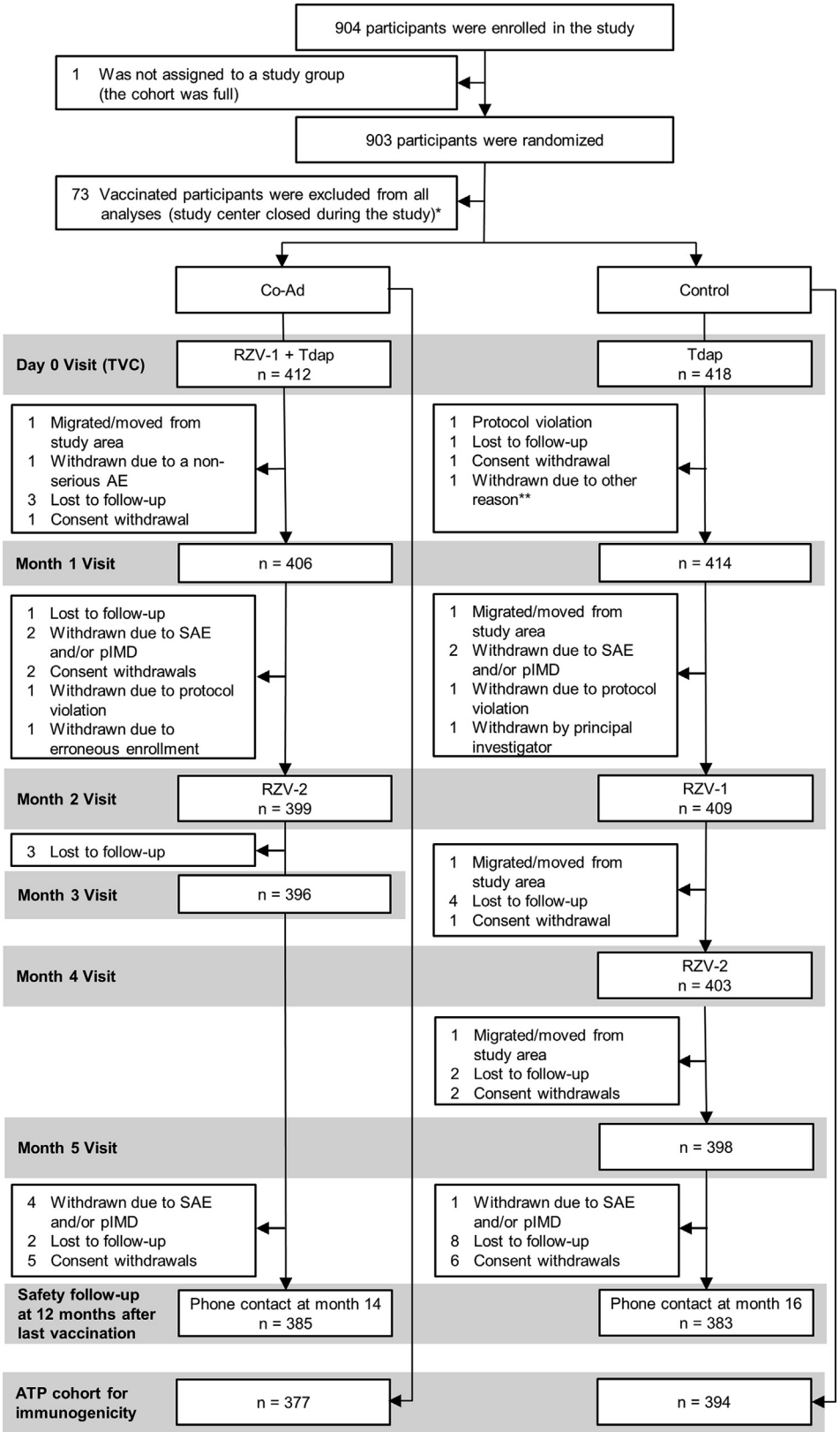

Fig. 1. Participant flow diagram. Tdap, reduced-antigen-content diphtheria-tetanus-acellular pertussis vaccine; RZV, adjuvanted recombinant zoster vaccine; RZV-1, RZV dose 1; RZV-2, RZV dose 2; Co-Ad, study group in which participants received the RZV dose 1 and Tdap co-administered at Day 0 and the RZV dose 2 at Month 2; Control, study group in which participants received Tdap at Day 0, the RZV dose 1 at Month 2 and RZV dose 2 at Month 4; n, number of participants attending the corresponding visit; TVC, total vaccinated cohort; ATP, according-to-protocol; (S)AE, (serious) adverse event; pIMD potential immune-mediated disease. *In the study center that closed in August 2014 due to business reasons, 73 participants were enrolled and vaccinated prior to closure. Of these, 32 consented to transfer to another center and were followed for limited safety only (SAEs, pIMDs, pregnancies and herpes zoster cases) until the end of the study. All samples collected from the 73 participants were destroyed. These 73 participants were excluded from all analyses as the data collected could not be validated by the investigator. 76 other eligible adults were subsequently enrolled to compensate this exclusion. **This participant withdrew from the study due to a combination of pre-existing irritable bowel syndrome and time constraints associated with employment.

Table 1
Demographic characteristics of study participants (total vaccinated cohort).

Characteristic	Parameters/Categories	Co-Ad N = 412		Control N = 418	
		Value or n	%	Value or n	%
Age (years)*	Mean ± SD	63.4 ± 8.4		63.1 ± 9.0	
Gender	Female	222	53.9	225	53.8
	Male	190	46.1	193	46.2
Geographic ancestry	Caucasian/European	364	88.3	357	85.4
	African Heritage/African American	41	10.0	53	12.7
	Other	7	1.7	8	1.9

Co-Ad, study group in which participants received the adjuvanted recombinant zoster vaccine (RZV) dose 1 and the reduced-antigen-content diphtheria-tetanus-acellular pertussis vaccine (Tdap) co-administered at Day 0 and the RZV dose 2 at Month 2; Control, study group in which participants received Tdap at Day 0, the RZV dose 1 at Month 2 and RZV dose 2 at Month 4; N, total number of participants; n (%), number (percentage) of participants in a given category; SD, standard deviation.
* At first study vaccination.

Table 2
Response to RZV and Tdap (according-to-protocol cohort for immunogenicity).

RZV response (1 month post-RZV dose 2)						
		Co-Ad		Control		$GMC_{Control}/GMC_{Co-Ad}$ (95% CI)
		N	Value	N	Value	Value
VRR, % (95% CI)		369	97.8 (**95.8**†–99.1)	378	97.9 (95.9–99.1)	–
Adjusted* anti gE GMC, mIU/mL (95% CI)		369	51178.8 (48003.0–54564.7)	378	56824.8 (53336.1–60541.6)	1.11 (1.02–**1.21**‡)
Tdap response (1 month post-Tdap vaccination)						
Response to pertussis antigens						
		Co-Ad		Control		$GMC_{Control}/GMC_{Co-Ad}$ (95% CI)
Adjusted** GMC, IU/mL (95% CI)	Antibody	N	Value	N	Value	Value
	Anti-FHA	373	315.3 (283.4–350.8)	391	392.2 (353.3–435.3)	1.24 (1.07–**1.44**‡)
	Anti-PT	371	43.6 (39.0–48.8)	389	50.9 (45.6–56.7)	1.17 (1.00–**1.36**‡)
	Anti-PRN	363	221.6 (189.7–258.8)	387	281.7 (242.4–327.4)	1.27 (1.02–**1.58**‡)
Response to diphtheria and tetanus antigens						
		Co-Ad		Control		$\%_{Control}–\%_{Co-Ad}$ (95% CI)
Percentage of participants with antibody concentrations ≥ 1.0 IU/mL	Antibody	N′	Value	N′	Value	Value
	anti-D	374	73.8	389	75.3	1.52 (−4.66–**7.72**¥)
	anti-T	374	96.5	394	95.7	−0.84 (−3.73–**2.02**¥)

VRR, percentage of participants who had at least: (i) a 4-fold increase in the post-RZV dose 2 anti-gE antibody concentration compared to the anti-gE cut-off (97 mIU/mL) for participants who were seronegative at baseline, or (ii) a 4-fold increase in the post-RZV dose 2 anti-gE antibody concentration compared to the pre-RZV vaccination anti-gE concentration for participants who were seropositive at baseline.
Co-Ad, study group in which participants received the adjuvanted recombinant zoster vaccine (RZV) dose 1 and the reduced-antigen-content diphtheria-tetanus-acellular pertussis vaccine (Tdap) co-administered at Day 0 and the RZV dose 2 at Month 2; Control, study group in which participants received Tdap at Day 0, the RZV dose 1 at Month 2 and RZV dose 2 at Month 4; VRR, vaccine response rate; gE, glycoprotein E; GMC, geometric mean concentration; FHA, filamentous hemagglutinin; PT, pertussis toxin; PRN, pertactin; D, diphtheria; T, tetanus; IU, international units; mIU, milli IU; N, number of participants with both pre- and post-vaccination results available; N′, number of participants with available post-vaccination results; CI, confidence interval.
* Adjusted for baseline concentration and age.
** Adjusted for baseline concentration.
† Success criterion: lower limit of 95% CI ≥ 60%.
‡ Non-inferiority criterion: upper limit of 2-sided 95% CI < 1.5.
¥ Non-inferiority criterion: upper limit of 2-sided 95% CI < 10%.

The non-inferiority criterion (UL of 95% CI <10%) for the humoral immune response to Tdap in the Co-Ad versus the Control group was met for anti-D and anti-T (Table 2).

3.3. Reactogenicity and safety

Overall, the percentage of participants reporting solicited local or general symptoms was similar in the Co-Ad and Control groups (Table 4).

The most common solicited local symptom after vaccination was pain, reported after RZV by 83.3% (8.4% grade 3) and 85.4% (9.2% grade 3) of participants in the Co-Ad and Control groups, respectively (Fig. 2A). After Tdap vaccination, pain was reported by 45.1% (2.0% grade 3) and 38.1% (0.7% grade 3) of participants in the Co-Ad and Control groups, respectively (Fig. 2B). The median duration of solicited local symptoms reported per dose was 3 days or less.

Overall, the most common solicited general symptom was myalgia followed by fatigue. Myalgia was reported by 55.8% (6.6% grade 3) and 59.0% (7.8% grade 3), while fatigue by 45.7% (7.4% grade 3) and 46.6% (6.6% grade 3) of participants in the Co-Ad and Control groups, respectively (Fig. 2C). The median duration of solicited general symptoms reported per dose was 2 days or less.

Within 30 days after vaccination, unsolicited AEs were reported by 105 (25.5%) and 118 (28.2%) participants in the Co-Ad and Control groups, respectively. Of these, 27 Co-Ad group and 31 Control group participants reported unsolicited AEs assessed by the investigator to be causally related to vaccination (Table 4). These included one grade 3 injection site pruritus and one grade 3 syncope in the Co-Ad group, and one grade 3 viral upper respiratory tract infection and one grade 3 cough in the Control group. The

Table 3
Pre- and post-vaccination antibody GMCs and seropositivity rates (according-to-protocol cohort for immunogenicity).

	Co-Ad			Control		
Timing	N	% Seropositive (95% CI)	GMC (95% CI)	N	% Seropositive (95% CI)	GMC (95% CI)
Anti-gE (seropositivity threshold: 97 mIU/mL)						
Pre-RZV	376	98.9 (97.3–99.7)	1317.9 (1190.4–1459.1)	386	99.0 (97.4–99.7)	1458.6 (1318.7–1613.2)
Post-RZV	369	100 (99.0–100)	51687.7 (48425.1–55170.1)	380	100 (99.0–100)	57998.6 (54456.9–61770.6)
Anti-FHA (seropositivity threshold: 2.046 IU/mL)						
Pre-Tdap	377	98.7 (96.9–99.6)	26.0 (23.1–29.3)	394	98.7 (97.1–99.6)	30.3 (27.1–34.0)
Post-Tdap	373	100 (99.0–100)	309.3 (276.4–346.0)	391	100 (99.1–100)	399.4 (359.1–444.3)
Anti-PT (seropositivity threshold: 2.693 IU/mL)						
Pre-Tdap	374	66.6 (61.5–71.3)	5.1 (4.5–5.8)	389	73.0 (68.3–77.4)	6.4 (5.6–7.2)
Post-Tdap	374	96.8 (94.5–98.3)	41.1 (36.2–46.7)	394	97.5 (95.4–98.8)	53.9 (47.4–61.4)
Anti-PRN (seropositivity threshold: 2.187 IU/mL)						
Pre-Tdap	369	90.0 (86.4–92.8)	18.4 (15.5–21.9)	388	89.2 (85.7–92.1)	17.3 (14.7–20.5)
Post-Tdap	370	99.2 (97.6–99.8)	222.6 (186.3–266.0)	392	98.5 (96.7–99.4)	278.1 (232.9–332.0)
Anti-D (seropositivity threshold: 0.057 IU/mL)						
Pre-Tdap	365	89.0 (85.4–92.1)	0.4 (0.4–0.5)	383	87.5 (83.7–90.6)	0.4 (0.3–0.4)
Post-Tdap	374	96.0 (93.5–97.7)	2.2 (1.9–2.6)	389	95.9 (93.4–97.6)	2.5 (2.1–3.0)
Anti-T (seropositivity threshold: 0.043 IU/mL)						
Pre-Tdap	376	94.7 (91.9–96.7)	1.4 (1.2–1.7)	393	94.4 (91.6–96.5)	1.4 (1.2–1.7)
Post-Tdap	374	99.7 (98.5–100)	8.7 (7.8–9.7)	394	99.7 (98.6–100)	10.1 (9.0–11.4)

Co-Ad, study group in which participants received the adjuvanted recombinant zoster vaccine (RZV) dose 1 and the reduced-antigen-content diphtheria-tetanus-acellular pertussis vaccine (Tdap) co-administered at Day 0 and the RZV dose 2 at Month 2; Control, study group in which participants received Tdap at Day 0, the RZV dose 1 at Month 2 and RZV dose 2 at Month 4; gE, glycoprotein E; GMC, geometric mean concentration; FHA, filamentous hemagglutinin; PT, pertussis toxin; PRN, pertactin; D, diphtheria; T, tetanus; IU, international units; mIU, milli IU; N, number of participants with available results; CI, confidence interval; pre-RZV, before RZV dose 1; post-RZV, 1 month post-RZV dose 2; pre-Tdap, before Tdap vaccination; post-Tdap, 1 month post-Tdap vaccination.

Table 4
Reactogenicity and safety after RZV and Tdap vaccination (total vaccinated cohort, overall/participant).

	Co-Ad		Control	
	n	% (95% CI)	n	% (95% CI)
Within 7 days after vaccination	N = 407		N = 412	
Any solicited local symptom	358	88.0 (84.4–91.0)	360	87.4 (83.8–90.4)
Grade 3 solicited local symptom	45	11.1 (8.2–14.5)	46	11.2 (8.3–14.6)
Any solicited general symptom	296	72.7 (68.1–77.0)	307	74.5 (70.0–78.7)
Grade 3 solicited general symptom	60	14.7 (11.4–18.6)	59	14.3 (11.1–18.1)
Within 30 days after vaccination	N′ = 412		N′ = 418	
Any unsolicited adverse event	105	25.5 (21.3–30.0)	118	28.2 (24.0–32.8)
Considered related	27	6.6 (4.4–9.4)	31	7.4 (5.1–10.4)
Grade 3 unsolicited adverse event	10	2.4 (1.2–4.4)	15	3.6 (2.0–5.8)
Considered related	2	0.5 (0.1–1.7)	2	0.5 (0.1–1.7)
From first vaccination up to study end*	N′ = 412		N′ = 418	
Any serious adverse event	21	5.1 (3.2–7.7)	31	7.4 (5.1–10.4)
Considered related	0		0	
Potential immune-mediated disease	0		0	

Co-Ad, study group in which participants received the adjuvanted recombinant zoster vaccine (RZV) dose 1 and the reduced-antigen-content diphtheria-tetanus-acellular pertussis vaccine (Tdap) co-administered at Day 0 and the RZV dose 2 at Month 2; Control, study group in which participants received Tdap at Day 0, the RZV dose 1 at Month 2 and RZV dose 2 at Month 4; N, number of participants with at least one administered dose documented; N′, number of participants with at least one administered dose; n, number of participants with at least one event across doses; 95% CI, confidence interval.

* 14 and 16 months after first vaccination in Co-Ad and Control groups, respectively.

most frequently reported unsolicited AEs of any grade were injection site pruritus in the Co-Ad group (2.4% of participants), and injection site pruritus and viral upper respiratory tract infection in the Control group (1.9% of participants each). During the entire study period, SAEs were reported by 21 (5.1%) and 31 (7.4%) participants in the Co-Ad and Control groups, respectively (Table 4). No SAEs were assessed by the investigator to have a causal relationship to study vaccination. During the study, 4 deaths occurred in each of the study groups, none of which were considered related to vaccination. No pIMDs were reported from first vaccination until study end.

One suspected HZ case was reported for a participant in the Co-Ad group 256 days after administration of RZV dose 2. This HZ episode was assessed by the investigator as not causally related to vaccination and it resolved in 8 days.

4. Discussion

This study evaluated the humoral immunogenicity and safety of RZV and Tdap vaccines when they were administered concurrently or sequentially. Co-administration of RZV and Tdap induced strong immune responses to the 6 antigens evaluated. While non-inferiority criteria were met for the humoral response to RZV and for 4 Tdap antigens, immunological non-inferiority was not demonstrated for the immune response to the pertussis antigen

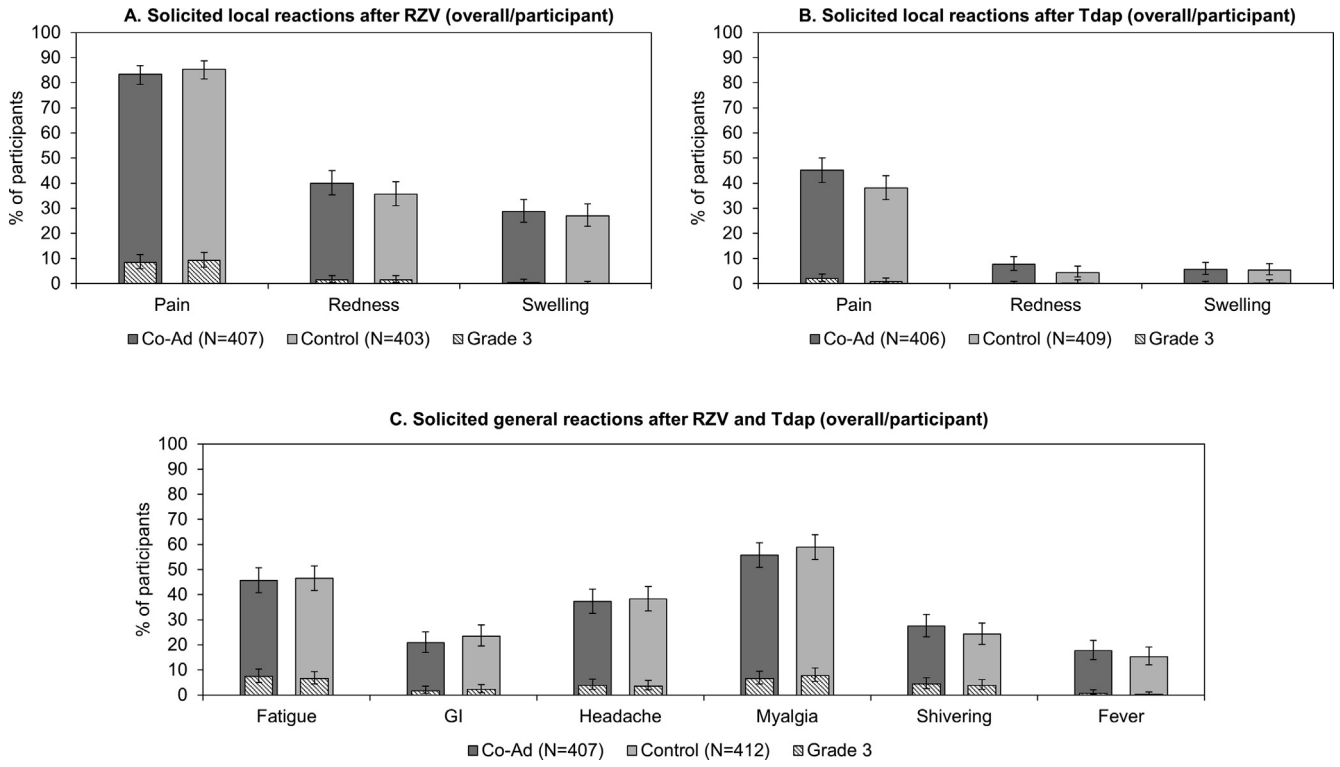

Fig. 2. Solicited adverse events after vaccination (total vaccinated cohort). Tdap, reduced-antigen-content diphtheria-tetanus-acellular pertussis vaccine; RZV, adjuvanted recombinant zoster vaccine; Co-Ad, study group in which participants received the RZV dose 1 and Tdap co-administered at Day 0 and the RZV dose 2 at Month 2; Control, study group in which participants received Tdap at Day 0, the RZV dose 1 at Month 2 and RZV dose 2 at Month 4; GI, gastrointestinal symptoms: nausea, vomiting, diarrhea and/or abdominal pain; N, number of participants with at least one administered dose documented. Error bars depict 95% confidence intervals.

PRN. Per protocol, co-administration would have been considered non-inferior only if all co-primary objectives were met.

The VRR to RZV in the Co-Ad group was 97.8% (97.9% in the Control group), and the anti-gE responses to two doses of RZV were similar in the Co-Ad and Control groups at 1M post-RZV dose 2. Furthermore, in both groups, the immunogenicity of RZV, assessed 1M post-RZV dose 2, was consistent with findings of previous phase II and III trials [14,33–35]. In line with our findings, immunogenicity of RZV was not affected by the co-administration of other vaccines [29,30].

For anti-D and anti-T, an antibody concentration of 0.1 IU/mL (ELISA) provides a conservative estimate of protective threshold [36,37]. For both anti-D and anti-T concentrations, the non-inferiority criterion for co-administration was met. In addition, one month post-Tdap vaccination, 73.8% and 96.5% participants from the Co-Ad group had anti-D and anti-T antibody concentrations ≥1.0 IU/mL (i.e., ≥10-fold the protective threshold), respectively.

Although there is no unequivocal correlate of protection against pertussis [38], efficacy of pertussis antigen-containing vaccines such as Tdap or the diphtheria-tetanus-acellular pertussis vaccine (DTaP) has been inferred in previous studies [39,40] by bridging immune responses for the pertussis antigens PT, FHA, and PRN to those reported in a German Household Contact Study [41], in which DTaP demonstrated >88% efficacy against pertussis [42]. The immune responses to these three pertussis antigens in the Co-Ad group compare favorably to the levels observed in the household contact study participants following a 3rd DTaP dose (Fig. 3) [41]. Taken together, these data do not suggest a clinically relevant interference between RZV and Tdap.

The failure to demonstrate immunological non-inferiority for humoral responses to all pertussis antigens has been described in other co-administration settings where the DTaP or Tdap was co-administered with the trivalent influenza vaccine, the tetravalent meningococcal conjugate vaccine, and the quadrivalent meningococcal tetanus toxoid conjugate vaccine [39,40,43]. Immune interference from co-administration remains one potential etiology for the failure to demonstrate non-inferiority for PRN.

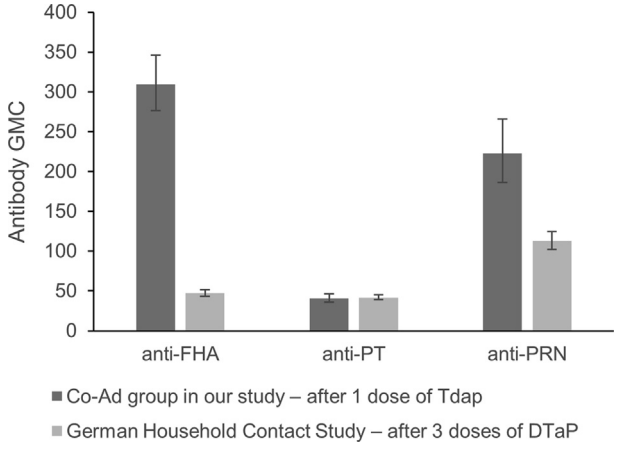

Fig. 3. Antibody responses to pertussis antigens in the Co-Ad group (according-to-protocol cohort for immunogenicity) compared to the German Household Contact Study (total vaccinated cohort). Tdap, reduced-antigen-content diphtheria-tetanus-acellular pertussis vaccine; DTaP, diphtheria-tetanus-acellular pertussis vaccine; FHA, filamentous hemagglutinin; PT, pertussis toxin; PRN, pertactin; GMC, geometric mean concentration; Co-Ad, study group in which participants received the adjuvanted recombinant zoster vaccine (RZV) dose 1 and Tdap co-administered at Day 0 and the RZV dose 2 at Month 2. Error bars depict 95% confidence intervals. Legacy enzyme-linked immunosorbent assays (ELISAs) used in the German Household Contact Study (GHCS [41]) were converted into estimations of contemporary ELISAs using imputation methodology using results of samples tested with both previous and contemporary assays. The GMCs from the GHCS used for this comparison are based on these imputed new ELISA results [44].

No safety concerns were identified in this study. Safety and reactogenicity profiles were similar when RZV and Tdap were co-administered or given sequentially. These observations are consistent with findings of previous co-administration studies with RZV [29,30]. The slightly higher number of participants reporting SAEs in the Control group may reflect the longer follow-up period imposed by the study design. Safety and reactogenicity of RZV were generally consistent with the results from previous phase II and III studies [12,13,33,34].

As older adults might face barriers to immunization, such as the burden of visits to a healthcare professional for the sole purpose of a vaccination and the lack of awareness of the importance of vaccination in this population segment, the opportunity for co-administration of these two vaccines at the same visit may lead to increased compliance with RZV and Tdap vaccination recommendations in adults aged ≥50 years. Overcoming barriers to adult immunization, including generating immunogenicity and safety data for vaccine co-administration, is a key component of furthering adult vaccination as a public health strategy.

The results of this study should be interpreted considering its limitations. The open label design of the study might have introduced bias in the assessment of safety. As injection site reactions in the dominant arm may interfere more with daily activities, the relative reactogenicity of the vaccines should be interpreted with caution. Safety outcomes should also be interpreted knowing that the Co-Ad and Control groups did not follow the same study schedule (two versus three vaccination visits, respectively) and Co-Ad participants were followed until M14 while Control participants followed until M16.

A plain language graphical summary contextualizing the results and potential clinical research relevance and impact is displayed in the Focus on Patient Section (Supplementary Fig. 1).

5. Conclusions

In a clinical trial where the first dose of RZV was given concomitantly with Tdap compared to when both vaccines were administered sequentially, immunogenicity non-inferiority criteria were met for all vaccine antigens with the exception of the humoral response to the pertussis antigen, PRN. However, as PRN-specific immune responses in the Co-Ad group compared favorably to protective levels in a German household contact study, these data do not suggest a clinically relevant interference between RZV and Tdap. Immunogenicity of RZV was not adversely impacted by co-administration with Tdap. No safety concerns were identified. The data from this study show that adults aged ≥50 years may receive RZV and Tdap concomitantly at the same visit and may support the advancement of adult vaccination as a public health strategy.

Funding

This work was supported by GlaxoSmithKline Biologicals SA in all stages of the study conduct and analysis. GlaxoSmithKline Biologicals SA also took responsibility for all costs associated with the development and publishing of the present manuscript.

Author's contributions

TCH and HL conceived and designed the study. LC, IE, HL, NS and AS collected or generated study data. LC, IE, TCH, HL, NS and AS performed the study. PB, LC, IE, TCH, HL, LO, AES and AS were involved in the analysis or interpretation of the data. All authors contributed to the writing/reviewing of the paper and approved the final version for submission.

Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: TCH, LO, and HL were employed by the GSK group of companies at the time this study was conceived, designed, initiated, and/or conducted. HL received salary and stock as part of his employee remuneration. TCH continues to own stock and stock options, and LO continues to own stock from the GSK group of companies. TCH and LO are inventors on a patent owned by the GSK group of companies and relevant to RZV. TCH was a paid consultant for the GSK group of companies during the development of this manuscript. HL is currently an employee of Pfizer and receives salary and stock as part of his employee remuneration. LO is employee of CureVacAG as of March 1st 2018. LC, PB, IE, AES and AS are employed by the GSK group of companies and receive salary as part of their employee remuneration. LC receives shares and AS and AES own stock options as part of their employee remuneration. NS reports grants from the GSK group of companies during the conduct of the study, and grants from Pfizer, Sanofi Pasteur and Novavax for work outside the submitted work.

Previous presentation

The data reported in this manuscript have not been presented previously.

Trademarks

Shingrix and Boostrix are trademarks of the GSK group of companies.

Acknowledgements

The authors would like to thank all study participants as well as all clinical investigators including: William Ellison (Radiant Research, Inc., South Carolina, United States), David Fried (Omega Medical Research, Rhode Island, United States), Paul Hartley (Uniontown, Pennsylvania, United States), John Hoekstra (National Clinical Research, Virginia, United States), Michael Levin (Clinical Research Centre of Nevada, Nevada, United States), George Raad (PMG Research of Charlotte, North Carolina, United States), Mark Turner (Advanced Clinical Research, Idaho, United States). Authors acknowledge Megan Riley for her critical review.

The authors would also like to thank Caroline Hervé for her contributions to the Zoster safety team, Marjan Hezareh for her contributions to the Zoster clinical team, and Toufik Zahaf for his contributions as lead statistician on the Zoster team (GSK, Wavre, Belgium). Immunogenicity data were generated by Clinical Laboratory Sciences under the supervision of Valérie Berthold (gE ELISA) and Sophie Van Damme (Tdap ELISA) (GSK, Rixensart, Belgium).

Medical writing services were provided by Alpár Pöllnitz (Modis on behalf of GSK). Editorial assistance and publication coordination were provided by Sara Blancquaert (Modis on behalf of GSK).

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.vaccine.2019.08.001.

References

[1] Dworkin RH, Johnson RW, Breuer J, Gnann JW, Levin MJ, Backonja M, et al. Recommendations for the management of herpes zoster. Clin Infect Dis 2007;44(Suppl 1):S1–S26. https://doi.org/10.1086/510206.

[2] Cohen JI. Clinical practice: herpes zoster. N Engl J Med 2013;369:255–63. https://doi.org/10.1056/NEJMcp1302674.
[3] Johnson RW. Herpes zoster and postherpetic neuralgia. Expert Rev Vaccines 2010;9:21–6. https://doi.org/10.1586/erv.10.30.
[4] Kawai K, Gebremeskel BG, Acosta CJ. Systematic review of incidence and complications of herpes zoster: towards a global perspective. BMJ Open 2014;4: e004833. https://doi.org/10.1136/bmjopen-2014-004833.
[5] Yawn BP, Gilden D. The global epidemiology of herpes zoster. Neurology 2013;81:928–30. https://doi.org/10.1212/WNL.0b013e3182a3516e.
[6] Johnson BH, Palmer L, Gatwood J, Lenhart G, Kawai K, Acosta CJ. Annual incidence rates of herpes zoster among an immunocompetent population in the United States. BMC Infect Dis 2015;15:502. https://doi.org/10.1186/s12879-015-1262-8.
[7] Gershon AA, Gershon MD, Breuer J, Levin MJ, Oaklander AL, Griffiths PD. Advances in the understanding of the pathogenesis and epidemiology of herpes zoster. J Clin Virol 2010;48(Suppl 1):S2–7. https://doi.org/10.1016/S1386-6532(10)70002-0.
[8] Harpaz R, Ortega-Sanchez IR, Seward JF. Prevention of herpes zoster: recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR Recomm Rep 2008;57:1–30. quiz CE2-4.
[9] Weinberg A, Zhang JH, Oxman MN, Johnson GR, Hayward AR, Caulfield MJ, et al. Varicella-zoster virus-specific immune responses to herpes zoster in elderly participants in a trial of a clinically effective zoster vaccine. J Infect Dis 2009;200:1068–77. https://doi.org/10.1086/605611.
[10] Oxman MN. Herpes zoster pathogenesis and cell-mediated immunity and immunosenescence. J Am Osteopath Assoc 2009;109:S13–7.
[11] Lecrenier N, Beukelaers P, Colindres R, Curran D, De Kesel C, De Saegher JP, et al. Development of adjuvanted recombinant zoster vaccine and its implications for shingles prevention. Expert Rev Vaccines 2018;17:619–34. https://doi.org/10.1080/14760584.2018.1495565.
[12] Lal H, Cunningham AL, Godeaux O, Chlibek R, Diez-Domingo J, Hwang SJ, et al. Efficacy of an adjuvanted herpes zoster subunit vaccine in older adults. N Engl J Med 2015;372:2087–96. https://doi.org/10.1056/NEJMoa1501184.
[13] Cunningham AL, Lal H, Kovac M, Chlibek R, Hwang SJ, Diez-Domingo J, et al. Efficacy of the herpes zoster subunit vaccine in adults 70 years of age or older. N Engl J Med 2016;375:1019–32. https://doi.org/10.1056/NEJMoa1603800.
[14] Cunningham AL, Heineman TC, Lal H, Godeaux O, Chlibek R, Hwang S-J, et al. Immune responses to a recombinant glycoprotein E herpes zoster vaccine in adults aged 50 years or older. J Infect Dis 2018;217:1750–60. https://doi.org/10.1093/infdis/jiy095.
[15] FDA. Shingrix prescribing information. Available at: <https://www.fda.gov/downloads/BiologicsBloodVaccines/Vaccines/ApprovedProducts/UCM581605.pdf> [accessed 20 Mar 2019].
[16] Health Canada. Summary basis of decision. Available at: <https://hpr-rps.hres.ca/reg-content/summary-basis-decision-detailTwo.php?linkID=SBD00377> [accessed 20 Mar 2019].
[17] EMA. Shingrix. Summary of product characteristics. Available at: <http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/004336/WC500246550.pdf> [accessed 20 Mar 2019].
[18] Dooling KL, Guo A, Patel M, Lee GM, Moore K, Belongia EA, et al. Recommendations of the advisory committee on immunization practices for use of herpes zoster vaccines. MMWR Morb Mortal Wkly Rep 2018;67:103–8. https://doi.org/10.15585/mmwr.mm6703a5.
[19] Ghebrehewet S, MacPherson P, Ho A. Influenza. BMJ 2016;355: i6258. https://doi.org/10.1136/bmj.i6258.
[20] Mullooly JP, Bridges CB, Thompson WW, Chen J, Weintraub E, Jackson LA, et al. Influenza- and RSV-associated hospitalizations among adults. Vaccine 2007;25:846–55. https://doi.org/10.1016/j.vaccine.2006.09.041.
[21] Stupka JE, Mortensen EM, Anzueto A, Restrepo MI. Community-acquired pneumonia in elderly patients. Aging Health 2009;5:763–74. https://doi.org/10.2217/ahe.09.74.
[22] Masseria C, Krishnarajah G. The estimated incidence of pertussis in people aged 50 years old in the United States, 2006–2010. BMC Infect Dis 2015;15:534. https://doi.org/10.1186/s12879-015-1269-1.
[23] 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.
[24] McQuillan GM, Kruszon-Moran D, Deforest A, Chu SY, Wharton M. Serologic immunity to diphtheria and tetanus in the United States. Ann Intern Med 2002;136:660–6. https://doi.org/10.7326/0003-4819-136-9-200205070-00008.
[25] Halperin SA, Sweet L, Baxendale D, Neatby A, Rykers P, Smith B, et al. How soon after a prior tetanus-diphtheria vaccination can one give adult formulation tetanus-diphtheria-acellular pertussis vaccine? Pediatr Infect Dis J 2006;25:195–200. https://doi.org/10.1097/01.inf.0000202082.56403.c4.
[26] Lee HJ, Choi JH. Tetanus-diphtheria-acellular pertussis vaccination for adults: an update. Clin Exp Vaccine Res 2017;6:22–30. https://doi.org/10.7774/cevr.2017.6.1.22.
[27] CDC. Epidemiology and prevention of vaccine-preventable diseases: pertussis. Available at: <https://www.cdc.gov/vaccines/pubs/pinkbook/pert.html> [accessed 20 Mar 2019].
[28] Liang JL, Tiwari T, Moro P, Messonnier NE, Reingold A, Sawyer M, et al. 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;67:1–44. https://doi.org/10.15585/mmwr.rr6702a1.
[29] Schwarz TF, Aggarwal N, Moeckesch B, Schenkenberger I, Claeys C, Douha M, et al. Immunogenicity and safety of an adjuvanted herpes zoster subunit vaccine coadministered with seasonal influenza vaccine in adults aged 50 years or older. J Infect Dis 2017;216:1352–61. https://doi.org/10.1093/infdis/jix481.
[30] Marechal C, Lal H, Poder A, Ferguson M, Enweonye I, Heineman TC, et al. Immunogenicity and safety of the adjuvanted recombinant zoster vaccine co-administered with the 23-valent pneumococcal polysaccharide vaccine in adults ≥50 years of age: a randomized trial. Vaccine 2018;36:4278–86. https://doi.org/10.1016/j.vaccine.2018.05.110.
[31] Clopper CJ, Pearson ES. The use of confidence or fiducial limits illustrated in the case of the binomial. Biometrika 1934;26:404–13. https://doi.org/10.1093/biomet/26.4.404.
[32] Newcombe RG. Interval estimation for the difference between independent proportions: comparison of eleven methods. Stat Med 1998;17:873–90.
[33] Chlibek R, Bayas JM, Collins H, de la Pinta ML, Ledent E, Mols JF, et al. Safety and immunogenicity of an AS01-adjuvanted varicella-zoster virus subunit candidate vaccine against herpes zoster in adults ≥50 years of age. J Infect Dis 2013;208:1953–61. https://doi.org/10.1093/infdis/jit365.
[34] Chlibek R, Smetana J, Pauksens K, Rombo L, Van den Hoek JA, Richardus JH, et al. Safety and immunogenicity of three different formulations of an adjuvanted varicella-zoster virus subunit candidate vaccine in older adults: a phase II, randomized, controlled study. Vaccine 2014;32:1745–53. https://doi.org/10.1016/j.vaccine.2014.01.019.
[35] McElhaney JE, Lal H, Cunningham AL, Levin MJ, Chlibek R, Diez-Domingo J, et al. Efficacy, immunogenicity and safety of an investigational subunit adjuvanted herpes zoster vaccine in adults aged 60 years and older: results from the ZOE-50 and ZOE-70 efficacy studies. Open Forum Infect Dis 2016;3:127. https://doi.org/10.1093/ofid/ofw194.40.
[36] Camargo ME, Silveira L, Furuta JA, Oliveira EP, Germek OA. Immunoenzymatic assay of anti-diphtheric toxin antibodies in human serum. J Clin Microbiol 1984;20:772–4.
[37] Melville-Smith ME, Seagroatt VA, Watkins JT. A comparison of enzyme-linked immunosorbent assay (ELISA) with the toxin neutralization test in mice as a method for the estimation of tetanus antitoxin in human sera. J Biol Stand 1983;11:137–44. https://doi.org/10.1016/S0092-1157(83)80038-9.
[38] WHO. Acellular pertussis vaccines. Available at: <http://www.who.int/biologicals/areas/vaccines/apertussis/en/> [accessed 20 Mar 2019].
[39] 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;5:858–66. https://doi.org/10.4161/hv.9961.
[40] Leonardi M, Latiolais T, Sarpong K, Simon M, Twiggs J, Lei P, et al. Immunogenicity and reactogenicity of Infanrix™ when co-administered with meningococcal MenACWY-TT conjugate vaccine in toddlers primed with MenHibrix™ and Pediarix™. Vaccine 2015;33:924–32. https://doi.org/10.1016/j.vaccine.2014.09.064.
[41] Schmitt HJ, Schuind A, Knuf M, Beutel K, Schulte-Wissermann H, Gahr M, et al. Clinical experience of a tricomponent acellular pertussis vaccine combined with diphtheria and tetanus toxoids for primary vaccination in 22,505 infants. J Pediatr 1996;129:695–701. https://doi.org/10.1016/s0022-3476(96)70152-x.
[42] Schmitt HJ, von Konig CH, Neiss A, Bogaerts H, Bock HL, Schulte-Wissermann H, et al. Efficacy of acellular pertussis vaccine in early childhood after household exposure. JAMA 1996;275:37–41. https://doi.org/10.1001/jama.1996.03530250041024.
[43] Weston WM, Friedland LR, Wu X, Howe B. Immunogenicity and reactogenicity of co-administered tetanus-diphtheria-acellular pertussis (Tdap) and tetravalent meningococcal conjugate (MCV4) vaccines compared to their separate administration. Vaccine 2011;29:1017–22. https://doi.org/10.1016/j.vaccine.2010.11.057.
[44] GSK. Clinical study register (study ID 208355/022) Available at: <https://www.gsk-studyregister.com/study/6176> [accessed 20 Mar 2019].