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Immunogenicity and safety of one dose of diphtheria, tetanus, acellular pertussis and poliomyelitis vaccine (Repevax®) followed by two doses of diphtheria, tetanus and poliomyelitis vaccine (Revaxis®) in adults aged ≥40 years not receiving a diphtheria- and tetanus-containing vaccination in the last 20 years☆

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ABSTRACT

Introduction: The immunogenicity and safety of one dose of Tdap-IPV (tetanus, diphtheria, acellular pertussis and inactivated poliomyelitis vaccine) and two doses of Td-IPV (tetanus, diphtheria and inactivated poliomyelitis vaccine) were assessed in adults who had not received a diphtheria- and tetanus-containing vaccine in the last 20 years.

Methods: This open-label, multicentre study was conducted in adults aged ≥40 years with no diphtheria- and tetanus-containing vaccine in the last 20 years. Participants received one dose of Tdap-IPV followed by two doses of Td-IPV (0, 1, 6 month schedule). Primary immunogenicity objectives: to demonstrate acceptable seroprotection rates (percentage of participants with antibody titre above threshold) post-dose 3 for diphtheria (≥0.1 IU/mL by seroneutralization assay [SNA]); tetanus (≥0.1 IU/mL by enzyme-linked immunosorbent assay [ELISA]); and poliomyelitis (≥8 1/dil by SNA); and to evaluate the percentage of participants with an antibody concentration ≥5 EU/mL (by ELISA) for pertussis antigens post-dose 1. Seroprotection rates were acceptable if the lower limit of the 95% confidence interval (CI) was >95%. Percentage of participants with basic clinical immunity against diphtheria (≥0.01 IU/mL) was also assessed. Safety (adverse events [AEs] and serious AEs) was assessed after each dose.

Results: Overall, 336 participants were included (mean age: 60.2 years). Post-dose 3 seroprotection rates were: diphtheria, 94.6% (CI 91.5–96.8); tetanus and poliomyelitis, 100% (CI: 98.8–100). Percentage of participants with an antibody titre ≥5 EU/mL against pertussis antigens was ≥95.8% for all five pertussis components. Basic clinical immunity against diphtheria was achieved in 100% (CI: 98.8–100) of participants. AEs were reported more frequently following vaccination with Tdap-IPV (post-dose 1: 65.3%) than with Td-IPV (post-dose 2: 48.3%; post-dose 3: 50.3%).

Conclusions: This study highlights the benefits of using Tdap-IPV followed by two doses of Td-IPV in an adult population to achieve maximal protection against diphtheria, tetanus, poliomyelitis and pertussis simultaneously.

Abbreviations: AE, adverse event; CI, confidence interval; eCRFs, electronic case report forms; ELISA, enzyme-linked immunosorbent assay; FHA, filamentous haemagglutinin; FIM2&3, fimbriae types 2 and 3; FAS, full analysis set; GMC, geometric mean antibody concentration; GMCR, geometric mean concentration ratio; GMT, geometric mean titres; GP, general practitioner; LLOQ, lower limit of quantitation; PP, per-protocol; PRN, pertactin; PT, pertussis toxoid; SAE, serious adverse event; SNA, seroneutralization assay; SPC, Summary of Product Characteristics; STIKO, Ständigen Impfkommission; Tdap-IPV, tetanus, diphtheria, acellular pertussis and inactivated poliomyelitis vaccine; Td-IPV, tetanus, diphtheria and inactivated poliomyelitis vaccine; WHO, World Health Organization.

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1. Introduction

Many diseases in adults are preventable by retaining high vaccination coverage and immunity levels throughout adulthood [1]. Waning antibody levels following immunization with some inactivated vaccines mean that booster vaccinations are required in adulthood to maintain protection against diseases including diphtheria, tetanus and pertussis [1–3]. Vaccine coverage in adults is poor because vaccine recommendations are not as widely applied in adulthood as in childhood, leaving many adults susceptible to infection [1,3,4].

A high proportion of diphtheria cases were reported in adults during an outbreak occurring in Eastern Europe in the 1990s. A lack of diphtheria booster vaccinations in adults, leading to the accumulation of susceptible adults, combined with declining vaccine coverage rates in children contributed to the resurgence [5]. The World Health Organization (WHO) assessed that control of diphtheria in Europe requires immunity in ≥75% of adults and ≥90% of children [6]. Pertussis is a major cause of cough in adults, and infected adults who have not received a booster vaccination against pertussis are the main source of infection among susceptible infants [7–10]. Individual protection against tetanus should also be maintained throughout life. In 2010, the overall confirmed tetanus case rate in Europe was low (0.02 per 100,000 population) [11]. However, most cases occurred in adults aged ≥65 years, probably due to waning antibody levels and a lack of booster vaccinations in adulthood [11].

Despite the importance of high vaccination coverage in adults, recommendations regarding the timing and number of doses of diphtheria- and tetanus-containing vaccine in adults who have not received a diphtheria- and tetanus-containing vaccine in the last 20 years remained unclear at the time this study was designed. A three-dose schedule of a diphtheria- and tetanus-containing vaccine was investigated in this study, consistent with previously reported studies evaluating diphtheria- and tetanus-containing vaccines in individuals who are not compliant with vaccination recommendations [12]. This is in line with French and German guidelines, which recommend a three-dose vaccination schedule in individuals with an unknown/undocumented vaccination history [13,14].

Repevax® (Sanofi Pasteur MSD, Lyon, France; manufactured by Sanofi Pasteur Ltd, Toronto, Canada; also licensed as Triaxis Polio® and Adacel Polio®) contains tetanus toxoid and low-dose diphtheria toxoid combined with acellular 5-component pertussis and inactivated poliomyelitis antigens (Tdap-IPV) [15]. Tdap-IPV is indicated for booster vaccination against diphtheria, tetanus, pertussis and poliomyelitis in individuals aged ≥3 years following primary immunization. Revaxis® (Sanofi Pasteur MSD, Lyon, France; manufactured by Sanofi Pasteur Ltd, Toronto, Canada) combines tetanus toxoid and low-dose diphtheria toxoid combined with inactivated poliomyelitis antigens (Td-IPV). Td-IPV is indicated for booster vaccination against diphtheria, tetanus and poliomyelitis in individuals aged ≥6 years following primary vaccination [16].

The aim of this study, performed in adults aged ≥40 years with no diphtheria- and tetanus-containing vaccine in the last 20 years, was to assess the immunogenicity and safety after each dose of a three-dose regimen consisting of one dose of Tdap-IPV followed by two doses of Td-IPV, administered in a 0, 1, and 6 month schedule.

2. Methods

This open-label, multicentre study was performed in 12 centres (general practitioner [GP] surgeries, vaccination centres and Clinical Investigation Centres in hospitals) across France and Germany, in accordance with the International Conference on Harmonisation Good Clinical Practice standards, the Ethical Principles for Medical Research Involving Human Subjects of the World Medical Association, Declaration of Helsinki, and local/national guidelines. The study was approved by an independent ethics committee in each country. All participants provided signed, informed consent.

2.1. Study population

The study population comprised healthy adults aged ≥40 years who had not received a diphtheria- and tetanus-containing vaccine within the last 20 years. Vaccination history was established by the investigator asking participants to check their own vaccination records. Participants were recruited via advertisements in GP surgeries, vaccination centres, hospitals and newspapers. Participants had to attend all visits and comply with study procedures. For France only, participants had to be affiliated to a health social security system. Participants were excluded if they had been diagnosed with pertussis during the preceding 10 years, had received any live or inactivated vaccine within 28 or 14 days, respectively, prior to the study or had participated in any clinical trial within 4 weeks prior to the study. Additionally, individuals who were pregnant, had any medical condition or treatment that could affect the immune system, unstable chronic illness, hypersensitivity to the study vaccine components, history of post-vaccination Guillain-Barré syndrome, brachial neuritis, encephalopathy, any neurological disorder, or any condition that would contraindicate intramuscular vaccination were excluded.

2.2. Study vaccination

All participants were scheduled to receive one dose of Tdap-IPV (Repevax®; batch number E1142-3) followed by two doses of Td-IPV (Revaxis®; batch number E0630-1) in a 0, 1 and 6 month schedule. Vaccines were administered intramuscularly in the deltoid muscle using a 16 mm (0.5 mm diameter) or a 25 mm (0.6 mm diameter) needle.

2.3. Participant assessments

Demographic characteristics and medical/vaccination history were documented and a physical examination was performed. Blood samples were taken pre-vaccination and 1 month post-vaccination. Assessments included antibody titres for diphtheria, tetanus and poliomyelitis at all timepoints, and antibody titres for each of the five pertussis components (pertussis toxoid [PT], filamentous haemagglutinin [FHA], pertactin [PRN], and fimbriae types 2 and 3 [FIM2&3]) prior to vaccination and post-dose 1. Adverse events (AEs) were recorded up to 28 days after each vaccination. Serious AEs (SAEs) were documented throughout the study. Immediate AEs (within 20 min of vaccination) were reported by the investigator using electronic case report forms (eCRFs). After this period, solicited (Day 0–7) and unsolicited (Day 0–28) injection site and systemic AEs were reported by the participants using diary cards. AEs were determined by the investigator when reviewing the diary cards and were recorded in the eCRF.

2.4. Vaccine immunogenicity

2.4.1. Serological testing

Serological tests were conducted at the Global Clinical Immunology platform of Sanofi Pasteur Inc. (Swiftwater, PA, USA) without knowledge of the vaccine administered.

Antibodies to diphtheria were measured by the ability of test sera to protect Vero cells from diphtheria toxin challenge