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A Phase III randomised trial of the immunogenicity and safety of quadrivalent versus trivalent inactivated subunit influenza vaccine in adult and elderly subjects, assessing both anti-haemagglutinin and virus neutralisation antibody responses

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ABSTRACT

Background: Trivalent influenza vaccines (TIVs) offer substantial protection against matching B-strains, however, protection against alternate-lineage B-strains may be enhanced by adding a second B-strain in quadrivalent influenza vaccines (QIVs). In this Phase III, double-blind, multicentre, randomised study, the immunogenicity and safety of subunit inactivated QIV versus TIV was assessed in adult (aged ≥18 to ≤60 years) and elderly (aged ≥61 years) subjects by analysing a combination of haemagglutinin inhibition (HI) and virus neutralisation (VN).

Methods: Subjects (n = 1980) were recruited off season (2015/2016) from 20 centres in five European countries and randomised to receive either QIV (n = 1538), TIV with B-strain of the Victoria lineage (n = 221) or TIV with B-strain of the Yamagata lineage (n = 221). The primary aim was to demonstrate non-inferiority of QIV to TIV for immunogenicity against matched influenza strains based on post-vaccination HI titres. Secondary aims were to show superiority of QIV to TIV for immunogenicity against alternate-lineage B-strains and to characterise the immune response by reverse cumulative distribution (RCD) curves of antibody titres and derived serological parameters for HI and VN. Reactogenicity and occurrence of adverse events were assessed post-vaccination.

Results: QIV elicited a non-inferior immune response for matched strains (upper limit of 95% CI for HI geometric mean ratios [GMRs] <1.5) and a superior response for alternate-lineage B-strains (HI GMRs < 1; $p < 0.0001$) versus TIV. RCD curves demonstrated that post-vaccination HI and VN titres were higher for QIV versus TIV for both alternate-lineage B-strains. Seroconversion rates and geometric mean fold increases of the VN assay were consistent with the HI assay for all strains in QIV. Reporting rates of local and systemic reactions were similar in both vaccine groups.

Conclusions: QIV was non-inferior in immunogenicity to TIV for matched strains and superior to the alternate-lineage B-strains in TIV. Safety and tolerability profiles of QIV and TIV were comparable.

1. Introduction

Influenza is a respiratory infection caused by influenza viruses that affects all ages, which can lead to serious complications in high-risk individuals [1]. In temperate climates, seasonal influenza epidemics occur during the winter months and are associated with significant morbidity, mortality and economic burden [1–3]. Influenza A/H1N1, A/H3N2 and B viruses are currently circulating and can cause seasonal influenza outbreaks, with B viruses responsible for a median of 17% of influenza cases between 2000 and 2015 in Europe [4]. The disease burden of both A and B viruses is substantial, and B viruses have been estimated to be associated with 25% of all influenza related mortality [3,5]. Two antigenically distinct lineages of influenza B viruses (Victoria and Yamagata) co-circulate globally with levels of each lineage varying in different regions within the same influenza season [6–8]. Vaccination remains the most effective method of preventing influenza; further

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to this, the World Health Organization's Global Influenza Surveillance and Response System recommends the composition of vaccines based on the circulating influenza strains each influenza season both in the northern and southern hemisphere [1].

Trivalent influenza vaccines (TIVs), such as Influvac® (influenza vaccine, surface antigen, inactivated; Abbott Biologicals B.V., Weesp, The Netherlands), are currently widely available and contain two subtypes of influenza A (A/H1N1 and A/H3N2) and a single-type influenza B-strain (either Victoria or Yamagata lineage). TIVs have been shown to offer a high level of protection against matched-lineage influenza B-strains with proven immunogenicity and safety [9–11]. However, as TIVs contain only one B-strain, mismatch can occur between the recommended lineage for TIV and the circulating B-strain [5]. Although TIVs provide some cross-protection for alternate-lineage strains, quadrivalent influenza vaccines (QIVs) containing B-strains from both the Victoria and Yamagata lineages have been developed to prevent mismatch [12]. Recent Phase III randomised clinical trials have demonstrated superiority of QIVs versus TIVs for immunogenicity of alternate-lineage B-strains and non-inferiority of QIVs versus TIVs for immunogenicity of shared-lineage vaccine strains [13–17].

Traditionally, the haemagglutinin inhibition (HI) assay has been the most important serological method used to investigate the immunogenicity of influenza vaccines [18,19]. It measures the antibodies against the haemagglutination antigen and correlates with the ability of antibodies to inhibit virus infection of host cells [19,20]. A serum HI titre of ≥40 is associated with a 50% reduction in susceptibility to influenza. However, as the HI assay detects antibodies solely against the influenza haemagglutinin protein, testing additional serological antigens or serological parameters may better assess vaccine effectiveness [20,21]. Consequently, the European Medicines Agency (EMA) now recommends the use of the virus neutralisation (VN) assay, which measures the levels of functional systemic antibodies to inhibit the cytopathic effects of the virus [20,22]. This assay provides valuable additional information, because it is more sensitive for some influenza strains, and detects additional virus antigens when compared with the HI assay [20]. To our knowledge, our study is the first to date to report VN as supplementary data to HI non-inferiority or superiority analyses in a Phase III clinical trial of QIV versus TIV in accordance with the new EMA guidelines on influenza vaccines [13–17].

In this Phase III, double-blind, multicentre, randomised study, the immunogenicity and safety of Abbott's candidate subunit inactivated QIV versus Influvac®, Abbott's subunit inactivated TIV, was assessed in adult (≥18 to ≤60 years of age) and elderly (≥61 years of age) subjects. The primary aim was to demonstrate the non-inferiority of QIV to TIV for shared-lineage influenza strains based on the post-vaccination HI-titres. Secondary aims were to show the superiority of QIV to TIV for alternate-lineage influenza B-strains and to characterise the immune responses in detail by means of reverse cumulative distribution (RCD) curves of antibody titres and derived serological parameters for HI and VN. The safety profile of QIV compared to that of TIV was assessed by analysing reactogenicity as well as the occurrence of unsolicited adverse events (AEs).

2. Materials and methods

2.1. Study design

This was a Phase III, randomised, double-blind, active-controlled, three-arm, multicentre study (EudraCT number: 2014-001042-24). Eligible subjects were randomly assigned to vaccination with QIV, TIV with B-strain of the Victoria lineage ($TIV_{(Vic)}$) or TIV with B-strain of the Yamagata lineage ($TIV_{(Yam)}$). Immunogenicity and safety were assessed at Day 22 (21 days post-vaccination) with a long-term safety follow-up period of 6 months. Written approval of the study was obtained from the relevant Independent Ethics Committee/Institutional Review Board. The study was conducted in compliance with Good Clinical Practice and all applicable laws and guidelines consistent with ethical principles of the Declaration of Helsinki [23].

2.2. Study subjects

Study subjects were adults (≥18 to ≤60 years of age) and elderly (≥61 years of age) stratified 1:1. The study included 20 centres in five European countries (Belgium, Germany, Hungary, Latvia and Lithuania) and consisted of two visits and two phone contacts per subject between May 2015 and January 2016. Male and female subjects were included if they could give informed consent, were ≥18 years of age on the day of vaccination and were in stable health. Exclusion criteria included: allergy to vaccine components; history of Guillain Barré syndrome; treatment with any vaccine within 4 weeks prior to the study vaccination or influenza vaccine within the 6 months preceding enrolment; immunocompromisation; a history of known drug or alcohol abuse or any other characteristic that, in the investigator's opinion, prohibited the inclusion of the subject into the study. Any medication that influenced the immune system was not permitted 4 weeks prior to the start of, or during, the study until the Day 22 assessment.

2.3. Randomisation and blinding

Subjects were randomly assigned to the three vaccine groups through an interactive web response system (randomisation scheme provided by Abbott Biologicals B.V.); randomisation was by country and age group. Vaccines were supplied as pre-filled syringes, and to achieve double-blindness, all syringes were identical in appearance. All study investigators and subjects remained blinded throughout the duration of the study; for emergency unblinding, an interactive web response system could be used.

2.4. Vaccines and vaccination schedule

Each subject received one 0.5 ml dose containing 15 μg of haemagglutinin for each virus strain by intramuscular injection (deltoid) using a 25 mm needle (QIV, 1095939-G54A; $TIV_{(Vic)}$, 1095937-G52; $TIV_{(Yam)}$, 1095938-G53). All study vaccines were manufactured by Abbott Biologicals B.V. Blood samples were taken at Day 1 (before vaccination) and at Day 22 (21 days post-vaccination).

2.5. Immunogenicity endpoints

The immunogenicity endpoints were Day 22 post-vaccination HI antibody titres and Day 22 post-vaccination VN antibody titres against the four virus strains.

2.5.1. Primary immunogenicity analysis

The non-inferiority of QIV to TIV with respect to induced immunogenicity against the shared strains was tested by comparing the Day 22 HI geometric mean titres (GMTs) of the shared strains between the QIV and TIV formulations in subjects ≥18 years of age (per-protocol sample [PPS]).

2.5.2. Secondary immunogenicity analysis

The superiority of QIV to TIV with respect to induced immunogenicity against the alternate-lineage B-strains was tested by comparing the Day 22 HI GMTs of the alternate-lineage B-strains between QIV and TIV formulations in subjects ≥18 years of age.

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