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Immunogenicity and safety of Southern Hemisphere inactivated quadrivalent influenza vaccine: a Phase III, open-label study of adults in Brazil

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ABSTRACT

The World Health Organization influenza forecast now includes an influenza B strain from each of the influenza B lineages (B/Yamagata and B/Victoria) for inclusion in seasonal influenza vaccines. Traditional trivalent influenza vaccines include an influenza B strain from one lineage, but because two influenza B lineages frequently co-circulate, the effectiveness of trivalent vaccines may be reduced in seasons of influenza B vaccine-mismatch. Thus, quadrivalent vaccines may potentially reduce the burden of influenza compared with trivalent vaccines.

In this Phase III, open-label study, we assessed the immunogenicity and safety of Southern Hemisphere inactivated quadrivalent influenza vaccine (*Fluarix*^{TM} *Tetra*) in Brazilian adults (NCT02369341). The primary objective was to assess hemagglutination-inhibition antibody responses against each vaccine strain 21 days after vaccination in adults (aged ≥18–60 years) and older adults (aged >60 years). Solicited adverse events for four days post-vaccination, and unsolicited adverse events and serious adverse events for 21 days post-vaccination were also assessed.

A total of 63 adults and 57 older adults received one dose of inactivated quadrivalent influenza vaccine at the beginning of the 2015 Southern Hemisphere influenza season. After vaccination, in adults and older adults, the hemagglutination-inhibition titers fulfilled the European licensure criteria for immunogenicity. In adults, the seroprotection rates with HI titer ≥1:40 were 100% (A/H1N1), 98.4% (A/H3N2), 100% (B/Yamagata), and 100% (B/Victoria); in older adults were 94.7% (A/H1N1), 96.5% (A/H3N2), 100% (B/Yamagata),

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and 100% (B/Victoria). Pain was the most common solicited local adverse events in adults (27/62) and in older adults (13/57), and the most common solicited general adverse events in adults was myalgia (9/62), and in older adults were myalgia and arthralgia (both 2/57). Unsolicited adverse events were reported by 11/63 adults and 10/57 older adults.

The study showed that inactivated quadrivalent influenza vaccine was immunogenic and well-tolerated in Brazilian adults and older adults.

Introduction

Traditional trivalent influenza vaccines (inactivated trivalent influenza vaccines [IIV3s] and live attenuated influenza vaccines [LAIV3s]) include two influenza A strains (A/H1N1 and A/H3N2) and one influenza B strain that are recommended annually for the Northern and Southern Hemispheres by the *World Health Organization* (WHO) based on global surveillance. However, in the early 1980s, two phylogenetically-distinct influenza B lineages (B/Yamagata and B/Victoria) emerged globally in humans.[1] In a report published by *The Global Influenza B Study* in 2015, it was estimated that based on 26 countries in both Hemispheres and inter-tropical regions between 2000 and 2013, the average rate of influenza B lineage mismatch with the seasonal vaccine was about 25%.[2]

Although data regarding the burden of influenza B in Latin America are limited, influenza B has circulated in Brazil during most seasons over the past decade and B lineage has been reported in some seasons.[3–7] Surveillance studies between 2001 and 2013 show that one B lineage predominated in 10 seasons, and co-circulation was found in 2002, 2008, and 2013.[5] During 2013, when the B/Victoria strain in the Southern Hemisphere seasonal vaccine was mismatched, the reported rate of influenza B mismatch with the vaccine was >91% in Brazil, 100% in São Paulo, and 52% in South America.[3–6]

In response to global reports of B lineage mismatch and the hypothesis that quadrivalent vaccine may reduce the burden of influenza disease compared with trivalent vaccine, for the first time in the 2012–2013 Northern Hemisphere influenza season, the WHO influenza forecast included an influenza B strain from each of the influenza B lineages.[8,9] By the 2014–2015 influenza season, various quadrivalent influenza vaccines had been launched globally, and depending upon the region and product, were licensed for use in adults and children from 6 months of age.[10–20]

This Phase III, open-label study was conducted to assess the immunogenicity and safety of Southern Hemisphere inactivated quadrivalent influenza vaccine (IIV4) in adults in Brazil.

Methods

This Phase III, open-label study assessed the immunogenicity and safety of IIV4 in adults (18–60 years) and older adults (>60 years). The study was conducted in two centers in Brazil in 2015. Eligible subjects were aged ≥18 years, were in stable health, and had not received any non-registered drug or vaccine within 30 days, or any investigational or approved influenza vaccine within six months of the first visit. All subjects provided written informed consent.

The study protocol, informed consent and other information requiring pre-approval were reviewed and approved by Comissão Nacional de Ética em Pesquisa. The study was conducted in accordance with Good Clinical Practice, the principles of the Declaration of Helsinki, and all regulatory requirements (NCT02369341).

Objectives

The primary objective was to assess vaccine immunogenicity based on hemagglutination-inhibition (HI) antibody responses against each vaccine strain 21 days after vaccination in adults and older adults. Immunogenicity outcome measures (defined below) were assessed according to the European Committee for Medicinal Products for Human Use (CHMP) licensure criteria for immunogenicity of influenza vaccines.[21] The secondary immunogenicity objective was to assess HI antibody responses in each age strata according to previous influenza vaccine history during the preceding influenza season (2014) and according to baseline serostatus.

Reactogenicity and safety were assessed as secondary objectives and included solicited adverse events (AEs) (reactogenicity) for four days post-vaccination and unsolicited AEs, serious AEs (SAEs) and medically-attended AEs (MAEs) for 21 days post-vaccination.

Vaccine

The inactivated split virion vaccine (*Fluarix*™ *Tetra*) was a thiomersal-free vaccine manufactured by GSK Vaccines in Dresden, Germany. One 0.5 mL dose contained 60 μg hemagglutinin antigen (HA) including each of the four vaccine strains recommended by WHO for the 2015 influenza season in the Southern Hemisphere: A/California/7/2009 (H1N1)pdm09-like strain [variant A/Christchurch/16/2010 (NIB-74xp)], A/Switzerland/9715293/2013 (H3N2)-like strain [variant A/Switzerland/9715293/2013 (NIB-88)], B/Phuket/3073/2013-like strain [B/Phuket/3073/2013] (Yamagata lineage), B/Brisbane/60/2008-like strain [B/Brisbane/60/2008] (Victoria lineage).

Pre-filled syringes contained one dose of IIV4 which was administered intramuscularly in the deltoid of the non-dominant arm.