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Original research

Immunogenicity and safety of an inactivated quadrivalent influenza vaccine candidate versus inactivated trivalent influenza vaccines in participants >/=3 years of age: A double-blind, randomized, parallel-controlled phase III clinical trial in China

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Abstract

Background. Viruses from two antigenically distinct influenza B strains have co-circulated since the mid-1980s, yet inactivated trivalent influenza vaccines (TIVs) with either the Victoria or Yamagata lineage could only provide limited protection from influenza B strain. Quadrivalent influenza vaccine (QIV) including both influenza B lineages can improve protection against circulating influenza B viruses.

Methods. Participants >/= 3 years of age were recruited, stratified by age, and then randomly allocated at a ratio of 2:1:1 to receive one-injection of the experimental QIV, TIV-Victoria (Vic) or TIV-Yamagata (Yam). The primary objective of this study was to demonstrate that the hemagglutination-inhibition (HI) antibodies induced by the QIV candidate are not inferior to the licensed TIVs.

Results. First, 3661 participants (1829 in QIV group and 916 in each TIV control group) received the inoculation. The QIV was found to be non-inferior to TIVs in terms of the geometric mean titers (GMTs) and seroconversion rates (SCRs) of the HI antibodies against shared strains 28 days after completion of inoculation, and was superior to the TIVs against the alternate B strain, which is absent from the TIVs. The occurrences of adverse events (AEs) post-vaccination were similar across the treatment groups, except for a lower incidence of fevers observed in TIV-Vic group(4.37%) compared to the QIV(7.88%) and TIV-Yam (7.93%) groups in participants above 60 years of age. A total of 37 serious adverse events (SAEs) were noted during the 6-month follow up, of which 18(0.98%) were reported from QIV group and 13(1.41%), 6 (0.66%)were reported in the TIV-Yam and TIV-Vic groups, respectively; however, none of the SAEs were considered to be related to the study vaccines.

Conclusion. The experimental QIV showed good immunogenicity and an acceptable safety profile.

Keywords. Quadrivalent influenza vaccine; Immunogenicity; Safety; Clinical trial; Seasonal influenza; Victoria lineage; Yamagata lineage

1. Introduction

Influenza is an acute and highlyinfectious respiratory disease that causes significant morbidity and mortality worldwide that, has constituted a serious hazard to human health and public health for decades. According to the World Health Organization (WHO) report, approximately three to five million people are infected with influenza virus with serious symptoms, causing 250 to 500 thousand deaths each year. [1, 2]

Since 1978, two lineages of influenza A and one lineage of influenza B have been used in annual seasonal influenza vaccines. The choice of the B strain included in the traditional trivalent influenza vaccine (TIV) depends on worldwide surveillance data and takes ongoing antigenic drift into consideration. [3] However, this process is complicated by the frequently occurring mismatch of B strain. Furthermore,two lineages of B virus may circulate simultaneously, and the traditional TIV with the mismatched predominant B virus provides limited vaccine protection.[4] During the 2010-2011 season in the United States, influenza B was considered to be responsible for more than 30% of all influenza-associated pediatric mortalities. [5] Furthermore, epidemics of influenza B were also thought to lead to higher rates of hospitalizations than influenza A, especially in children, and in patients with specific clinical syndromes, including myocarditis. [6, 7] Since 2013-2014, the WHO began to recommend that two lineages of influenza B strain should be added to influenza vaccine formulas for prevention during the epidemic season. [8]

In this phase III clinical trial, the immunogenicity and safety of a novel quadrivalent influenza vaccine (QIV) with an additional influenza B strain was measured by comparing its performance with two traditional TIVs.

2. Methods

2.1. Participants and Study design

This randomized, parallel-controlled, double-blind, non-inferiority Phase III clinical trial of a novel QIV was conducted in Lianyungang City from January 2016 to August 2016.

Participants eligible for the study included healthy children, adolescents and adults aged >/=3 years old and if they were female, they were not pregnant. Participants with temperatures >37.0°C, participants who were immunocompromised, allergic to any vaccine component, or had infectious diseases, congenital malformations, progressive disorders, serious chronic diseases, or coagulation disorders, and those who received any subunit vaccine or inactivated vaccines in the last 14 days were excluded from the study (a full list of the inclusion and exclusion criteria was listed in appendix 1). Before taking part in the study, written informed consent was provided by the parents or guardians for children or adolescent participants was required, or by the participants themselves if they were adults.

Permission for this trial was obtained from the Institutional Review Boards of the Jiangsu Provincial Centers for Disease Control and Prevention, and the trial was undertaken in compliance with Good Clinical Practice guidelines, the Declaration of Helsinki and Chinese regulatory requirements. Clinicaltrials. gov: NCT02710409.

2.2. Vaccines

The experimental QIVs were developed by Jiangsu GDK Biotechnology Co., Ltd. Each dose contained 60 μg of hemagglutinin antigen (HA) in total, 15μg of HA per strain (A/California/7/2009, A/Switzerland/9715293/2013, B/Brisbane/60/2008 and B/Phuket/3073/2013).

Positive controls were manufactured by Changsheng Biology Science & Technology Co. Ltd., Changchun, China. Each dose contained 15μg of each HA of two influenza A strains (A/California/7/2009, A/Switzerland/9715293/2013) and one influenza B strain (B/Brisbane/60/2008 for TIV-Victoria[Vic] or B/Phuket/3073/2013 for TIV-Yamagata [Yam]).

All vaccines, were opalescent off-white to grayish suspensions, provided in prefilled syringes (0.5 ml) and labeled with an identical number, but no further information was provided. One dose of QIV or TIV was injected into the non-dominant arm of each participant.

2.3 Randomization and blinding

A stratified randomization procedure based on various age groups (3-17 years, 18-59 years and >/=60 years) was performed according to a blocked randomization list (block=4). The whole randomization process was conducted by an independent statistician, using SAS (version 9.4). Participants from each subage group were stratified at a ratio of 2:1:1 to receive QIV, TIV-Vic or TIV-Yam. The appearance of packages of QIV, TIV-Vic, TIV-Yam was identical and labeled with an assigned code from the randomization list as the only identifier. We assigned an identical number to every eligible participant enrolled according to their sequence at enrollment, and then, the vaccine with the same number was injected. The staff who performed the randomizing had no role in any other activities of this study. The treatment allocation was masked from participants and investigators throughout the study period.

2.4. Immunogenicity

Blood samples were taken from each participant both before and 28 days after the inoculation. The immunogenic non-inferiority of the geometric mean titers (GMTs) and seroconversion rates (SCRs) against the shared strains was assessed. In addition, we evaluated the immunogenic superiority of the GMTs and SCRs against alternative B strains that were absent from the TIV (B/Phuket/3073/2013 for TIV-Vic and B/Brisbane/60/2008 for TIV-Yam) 28 days after vaccination. The seroprotection rates (SPRs) defined as the percentage of participants with a serum anti-HI antibody titer >/=1:40 [9] and the geometric mean fold increases (GMFIs) were calculated for each treatment group post-vaccination according to the subage groups. Scientists from the National Institutes for Food and Drug Control performed antibody titers measurements against the vaccine strains in the HI assay, following standardized procedures. [10]

2.5. Safety

Each participant was observed for at least 30 minutes at the clinic site after the injection and followed for 28 days. Safety data were collected from all participants receiving the experimental vaccine as solicited and unsolicited adverse events (AEs)

within 7 and 28 days after vaccination, respectively. Solicited AEs were classified as injection-site AEs, including induction, redness, pain, swelling and itching; and systemic AEs including fever, diarrhea, cough, nausea/vomiting, fatigue, muscle pain, and headache. We graded all AEs according to the scale issued by the Chinese Food and Drug Administration. [11]

All solicited AEs occurring within 7days after completion of inoculation were regarded as vaccine-related events. The causality of the unsolicited AEs was determined by blinded investigators. The serious adverse events (SAEs) were defined as those requiring inpatient hospitalization, resulting in life-threatening effects or death, significant disability or incapacity, and were recorded throughout the entire study period and extended to 6 months after vaccine administration.

2.6. Sample Size and Statistical Analysis

A sample size of 3664 (1832 in the QIV group and 916 in both TIV control groups) was calculated to obtain an overall power of 90% to demonstrate the primary objective of meeting the CPMP criterion in items of the SCR and GMT for the 4 vaccine strains. [9] An immunogenic non-inferiority hypothesis was supported when the upper limit of the two-sided 95% confidence interval (CI) for the SCR difference (TIV minus QIV) and GMT ratios (TIV divided by QIV) did not exceed 10% and 1.5, respectively.

The immunogenicity analyses were performed using the According to Protocol cohort, which includes participants receiving a vaccination, receiving assay results for at least 1 study vaccine antigen, and remaining in compliance within the study time requirements. The SCRs and SPRs were evaluated according to the CPMP criterion of the European Agency for the Evaluation of Medicinal Products (EMEA). [9] The criteria were fulfilled if the lower limit of the two-sided 95% CI of the SCR was >/=40% (aged 3-59 years) or >/=30% (aged >/=60 years), and the lower limit of the two-sided 95% CI of SPR was >/=70% (aged 3-59 years) and >/=60% (aged >/=60 years). The frequency of the AEs after vaccination was tabulated and compared across the groups using Fisher's exact or Chi-square tests.

3. Results

This study was conducted from January 2016 to August 2016. A total of 4069 participants were assessed for eligibility, and 3664 participants were enrolled and randomized (Figure 1). Of these participants, three withdrew the consent before the vaccination, and 3661 participants received the vaccination. All the 3661 participants were involved in the safety analysis cohort, while 3536 participants donated blood sample post-vaccination and were included for immunogenicity analyses. The demographic characteristics of all participants at enrollment are listed in Table 1, showing comparable age, sex, and BMI values across the groups.

3.1. Immunogenicity

The baseline immunity against the vaccine strains in terms of the GMTs was similar among the participants across different the treatment groups (Table 1). One dose of QIV elicited a substantial increase in the HI antibody titer in all age groups (Table 2).

The GMTs of the antibodies against the A/California/7/2009 strain, A/Switzerland/9715293/2013 strain, B/Brisbane/60/2008 strain and B/Phuket/3073/2013 strain were 485.33, 471.13, 82.86 and 179.62 in the QIV group, compared to 427.12, 430.12, 62.55 and 174.48 in the TIV groups, respectively. in participants between 3 and 17 years of age on day 28 post-vaccination. In participants between 18 and 59 years of age, the GMTs of the antibodies against these four strains were 332.23, 237.04, 61.13, 149.65 compared to 284.33, 258.76, 44.22 and 105.23 in the TIV groups, respectively. For elderly participants above 60 years of age, the values were 154.72, 462.79, 64.75 and 181.03 in the QIV group and 198.08, 470.64, 48.28 and 126.48 in the TIV groups. In all age groups, the GMTs of the antibodies to the shared strains elicited by the QIV were non-inferior to those elicited by TIV, with the GMT ratios between 0.70 and 1.09; the GMTs of the antibodies to the additional strain elicited by QIV were also superior to those elicited by TIV, with the GMT ratios between 0.13 and 0.53.

The SCRs of the antibodies against the A/California/7/2009 strain, A/Switzerland/9715293/2013 strain, B/Brisbane/60/2008 strain and B/Phuket/3073/2013 strain were 87.82, 75.65, 74.41 and 83.54 in the QIV group, compared to 87.12, 71.89, 67.64 and 78.35 in the TIV groups, respectively, in participants between 3 and 17 years of age, on day 28 post-vaccination, and all lower limits of the two-sided 95% CI for the SCRs of the four strains in QIV group were >/=40%. In participants between 18 and 59 years of age, the SCRs of the antibodies against these four strains were 91.29, 83.29, 70.35 and 81.65 compared to 89.63, 81.34, 59.35 and 67.27 in the TIV groups, respectively, and all lower limits of the Two-sided 95% CI for the SCRs of the four strains in the QIV group were >/=40%. In elderly participants above 60 years of age, the SCRs of the antibodies against these 4 vaccine strains were 84.19, 88.20, 70.38 and 84.41 in the QIV group, and 83.93, 85.71, 54.30 and 69.60 in the TIV groups, and all lower limits of the two-sided 95% CI for the SCRs of the four strains in the QIV group were >/=30%. In all age groups, the SCRs of the antibodies against the shared strains elicited by QIV were non-inferior to those elicited by TIV with SCR differences between -16.08 and -0.26; The SCRs of antibodies against the additional strain elicited by QIV were superior to those elicited by TIV with the SCR differences between -69.72 and -24.64 (table 3).

In participants between 3 and 17 years of age, the SPRs of antibodies against A/California/7/2009 strain, A/Switzerland/9715293/2013 strain, B/Brisbane/60/2008 strain and B/Phuket/3073/2013 strain were 94.93, 99.32, 78.58 and 94.02 in the QIV group, of which the lower limits of the two-sided 95% CI for the SPRs of the four strains in the QIV group were >/=70%. For participants between 18 and 59 years of age, the SPRs of the antibodies against these four strains above were 97.88, 98.35, 76.47 and 95.29, of which the lower limits of the two-sided 95% CI for the SPRs of the four strains in the QIV group were >/=70%. Meanwhile, in elderly participants above 60 years of age, the SPRs of the antibodies against these 4 strains were 88.42, 99.11, 75.50 and 95.77 in the QIV group, of which the lower limits of the two-sided 95% CI on the SPRs of the four strains in QIV group were >/=60%. The GMFI

Values of the antibodies against the A/California/7/2009 strain, A/Switzerland/9715293/2013 strain, B/Brisbane/60/2008 strain and B/Phuket/3073/2013 strain were 24.04, 9.22, 11.01 and 10.00 respectively in participants between 3 and 17 years of age, and 26.79, 10.85, 7.90 and 7.59 in participants between 18 and 59 years of age, while the values were 20.77, 14.79, 7.56 and 8.05 in elderly participants above 60 years of age.

In this study, the TIV controls induced HI antibodies directed to the B lineage strain which was absent from the vaccine with seroconversionrates (4.69% in TIV-Yam and 29.66% in TIV-Vic) in participants between 3 and 17 years of age. For participants between 18 and 59 years of age, the values are 17.73 in TIV-Yam and 57.01 in TIV-Vic. Meanwhile, in participants above 60 years of age, these numbers (19.82% in TIV-Yam and 55.66% in TIV-Vic) were much higher.

3.2. Reactogenicity and Safety

The overall number of injection-site and systematic solicited adverse events reported within 7 days after vaccination was 293 (16.02%), 132 (14.41%) and 151 (16.48%) respectively in the QIV, TIV-Yam, and TIV-Vic groups, and these were comparable across the treatment groups (Table 4).

Pain was the most common injection-site adverse reaction of the recipients of QIV or TIV, with an incidence of 3.57% and 3.94%, respectively. Most of the events were mild or moderate. Only one grade 3 pain event was reported from one participant in the QIV group. Other common injection-site adverse reactions were induration, redness and swelling (Table 4).

The most common systemic adverse reaction was fever, with incidences ranging from 15.66% to 16.38% in participants aged 3-17 years old, 6.55% to 9.09% in participants aged 18-59 years old and 3.49% to 5.03% in participants above 60 years of age. However, grade 3 fevers were reported in less than 1% of all participants. Other common systemic adverse reactions included diarrhea, coughing, nausea/vomiting, fatigue, muscle pain and headache (table 4).

The overall numbers of participants with at least one non-solicited AE within 28 days post vaccination were reported for 109 (5.96%), 46 (5.02%) and 61 (6.66%) in the QIV, TIV-Yam, TIV-Vic groups, respectively. Non-solicited symptoms were reported for less than 5% of the participants in all treatment groups. A total of 18(0.98%) SAEs were reported from the QIV group, 13(1.41%) from the TIV-Yam group and 6(0.66%) from the TIV-Vic group. All the serious adverse events were determined to be not related to the study vaccines (a full list of the SAEs is listed in appendix 4).

4. Discussion

The results from this study showed that the QIV candidate had a good immunogenicity profile. The QIV candidate demonstrated non-inferiority compared to the TIVs in terms of the GMTs and the SCRs of the HI antibodies against shared strains 28 days after completion of inoculation and was superior to the TIVs against the alternate B strain, which was absent from the TIVs. Our results suggest that this QIV with an additional B strain could be an optimal replacement for TIV-Yam or TIV-Vic, and may potentially increase protection against influenza B.

Considering that the QIV candidate contained 60 μg of the influenza antigen, it was supposed to induce stronger local reactogenicity compared to the TIV controls, which only contained 45 μg of the antigen per dose. However, in this trial, the QIV candidate was comparable to the TIV controls in items of the incidence of the solicited injections, and the systemic and unsolicited AEs. No significant safety concerns for the QIV were noted and none of the SAEs observed were considered to be related to QIV candidate. The reactogenicity and safety findings of this trial suggest that the additional 15 μg antigen in the QIV candidate did not impact its safety profile.

Both the immunogenicity and safety findings of the QIV candidate manufactured in China were consistent with previous studies conducted in the USA, Europe and Asia. [12-19] There is growing evidence that the inactivated QIV provide similar

protection against shared strains versus TIV, and with the additional B lineage strain, the QIV may provide improved protection against influenza B.

Influenza B in fections are thought to be associate with high risk of severe illness and hospitalization in children and adolescents. [20] However, influenza A is thought be related to higher rates of complications and deaths than influenza B in elderly adults. [20] In a modeling study conducted in the UK, hospitalized patients with viral respiratory diseases were surveyed. Influenza A was found to be the highest ranking burden among patients aged 16-64 years, and influenza B ranked fourth and second in those aged <16 years and > 65 years, respectively. [21] When the B-lineage was mismatched, or when two lineages of B virus were circulating simultaneously, the protection provided by TIV was reduced. [22-24] During the 2013-2014 influenza season, the WHO began to recommend that an additional lineage of influenza B should be added to the traditional TIV formula for influenza prevention during the epidemic season, reflecting their recognition about the potential benefits of QIV for reducing the risk of the influenza B disease. [25] A QIV with an additional B strain could reduce the risk of B lineage mismatch and could provide improved protection against influenza B. [26]

One limitation of this study it is that this is a single-center clinical trial with all the participants recruited from one area, so the generalizability of the results may be compromised. In addition, the sample size of this study may not be sufficient to reveal any the potential rare adverse reactions related to the investigated vaccines, Thus, further large-scale population studies are still needed after licensing of the QIV for the market. Another limitation of the trial is that the efficacy or effectiveness of the QIV was not assessed. Thus, the additional protection and reduction of the disease burden provided by the extra B strain in QIV should be investigated in the future.

5. Conclusion

In summary, the QIV candidate was safe and immunologically non-inferior to TIVs in a healthy Chinese population above 3 years of age, and can provide an optimal replacement for TIV-Yam or TIV-Vic on the market, could potentially

making agreat impact on the development of better influenza vaccines for use in the national immunization schedule. Moreover, the additional antigen did not compromise the safety profile of QIV; therefore, the QIV candidate is a viable alternative to TIV for use in participantsabove 3 years old, and could provide a great option toward lowering the burden of disease due to the unpredictable epidemics in China.

6. Key issues

- The QIV candidate was demonstrated to be non-inferior to TIVs in terms of the GMTs and SCRs of HI antibodies against shared strains 28 days after the completion of inoculation.
- The QIV candidate was demonstrated to be superior to TIVs against the alternate B strain which is absent from TIVs.
- The additional antigen in QIV seemed to have no impact on the safety profile compared with the TIVs.

Clinical Trials Registration. NCT02710409.

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Declaration of interest

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

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Reference annotations

* Of interest
** Of considerable interest

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****This article estimated the additional public health benefit of QIV compared with TIV by calculating the expected impact on influenza-related health outcomes (illness, hospitalization, and death) over ten influenza seasons (1999/2000-2008/2009). And get the conclusion that the Use of QIV could have reduced annual cases (range: 2200-970,000), hospitalizations (range: 14-8200), and deaths (range: 1-485) in the US. Adjusting production capacity for a fourth virus in QIV could have resulted in reduced overall influenza vaccine availability and net increases in influenza-associated outcomes.**
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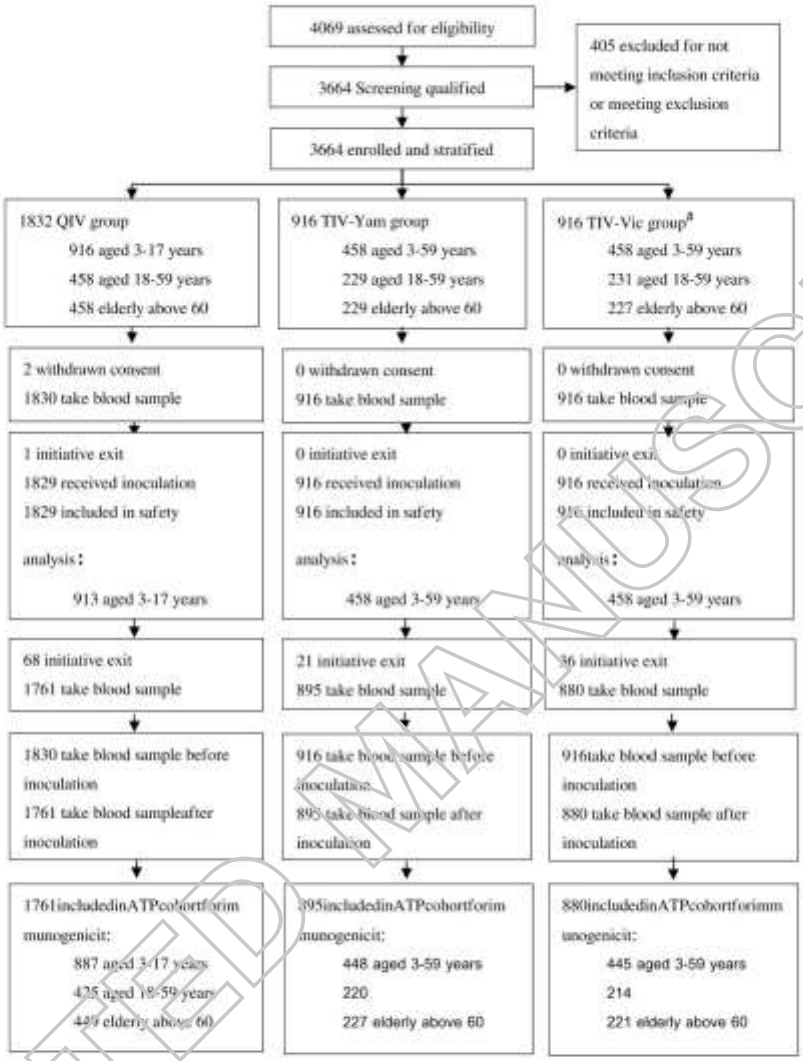

Figure 1. Trial profile. Abbreviation: QIV, Quadrivalent influenza vaccine; TIV, Trivalent influenza vaccine; ATP: According to Plan; PPS: Per protocol set;

[a]According to the randomization plan, there should be 687 participants in 3-59 group and 229 participants in >/= 60 group. Due to error made by our staff, two of 59 years old participants were assigned to >/= 60 group. When performing analysis, we grouped them according to their actual age.

Table 1. Demographic characteristics and immunogenicity at enrollment of QIV, TIV-Yam and TIV-Vic.

	Age 3-17 y			Age 18-59 y			≥60 y		
	QIV	TIV-Yam	TIV-Vic	QIV	TIV-Yam	TIV-Vic	QIV	TIV-Yam	TIV-Vic
N	916	458	458	459	229	231	457	229	227
Age in years (Mean; SD)	11.07±3.97	11.18±3.75	11.03±3.85	44.49±10.81	45.06±10.83	45.33±11.42	65.64±4.40	65.73±4.30	65.69±4.51
Male, n (%)	469(51.20)	234(51.09)	233(50.87)	205(44.66)	103(44.98)	103(44.59)	223(48.80)	112(48.91)	111(48.90)
Female, n (%)	447(48.80)	224(48.91)	225(49.13)	254(55.34)	126(55.02)	128(55.41)	234(51.20)	117(51.09)	116(51.10)
BMI (Mean; SD)	19.06±2.97	19.15±3.74	18.98±2.91	25.67±3.46	25.74±3.68	25.81±3.71	25.95±3.77	26.01±3.53	26.07±3.46
A/California/7/2009									
N	887	448	445	425	220	214	449	227	221
GMT Value(95%CI)	20.19(18.80-21.68)	20.28(18.45-22.29)	20.50(18.54-22.68)	12.40(11.31-13.60)	11.31(10.01-12.78)	11.95(10.52-13.58)	8.84 (8.17-9.57)	9.64(8.51-10.92)	8.90(7.97-9.94)
SPR%(95%CI)	36.98(33.79-40.25)	36.83(32.35-41.48)	37.98(33.45-42.67)	20.71(16.95-24.87)	14.55(10.17-19.91)	18.22(13.29-24.06)	10.91(8.18-14.17)	13.66(9.47-18.82)	12.67(8.59-17.79)
A/Switzerland/9715293/2013									
GMT Value(95%CI)	51.12 (47.34-55.21)	53.84(48.24-60.09)	59.04(53.00-65.78)	21.84(19.93-23.93)	21.44(18.81-24.42)	21.97(18.93-25.50)	31.29(28.34-34.56)	32.20(27.93-37.14)	33.66(28.53-39.72)
SPR%(95%CI)	69.00(65.84-72.03)	70.09(65.62-74.30)	73.71(69.36-77.74)	40.24(35.54-45.07)	40.00(33.47-46.80)	38.79(32.22-45.67)	51.67(46.94-56.38)	51.54(44.84-58.21)	52.49(45.68-59.23)
B/Brisbane/60/2008									
GMT Value(95%CI)	7.52(7.23-7.83)	7.66(7.23-8.13)	7.59(7.18-8.03)	7.74(7.32-8.19)	8.17(7.48-8.93)	7.47(6.93-8.05)	8.57(8.07-9.10)	8.58(7.80-9.44)	9.16(8.30-10.11)
SPR%(95%CI)	3.72(2.57-5.19)	4.69(2.92-7.08)	4.04(2.41-6.32)	3.06(1.64-5.17)	5.91(3.18-9.89)	2.34(0.76-5.37)	5.12(3.27-7.59)	7.05(4.08-11.19)	8.14(4.90-12.57)
B/Phuket/3073/2013									
GMT Value(95%CI)	17.96(16.96-19.01)	19.82(18.20-21.57)	18.10(16.71-19.61)	19.71(18.21-21.33)	19.81(17.63-22.26)	20.46(18.44-22.69)	22.49(20.74-24.39)	21.39(19.07-24.00)	22.25(19.60-25.27)
SPR%(95%CI)	29.99(26.99-33.12)	35.27(30.84-39.89)	28.99(24.81-33.45)	32.00(27.59-36.67)	33.64(27.42-40.30)	31.78(25.60-38.47)	36.75(32.28-41.39)	33.92(27.79-40.48)	32.13(26.02-38.72)

Abbreviations: QIV, quadrivalent influenza vaccine; SD, standard deviation; TIV-Vic, trivalent influenza vaccine Victoria lineage B strain; TIV-Yam, trivalent influenza vaccine Yamagata lineage B strain; SPR, seroprotection rate (defined as the percentage of subjects who had a serumanti-HI antibody titer ≥1:40); GMT, geometric mean titer;

Table 2. Immunogenicity of QIV, TIV-Yam and TIV-Vic.

	Age 3-17 y				Age 18-59 y				⩾60 y			
	QIV (N=887)	TIV-Yam (N=448)	TIV-Vic (N=445)	TIV-Yam+TIV-Vic(N=893)	QIV (N=425)	TIV-Yam (N=220)	TIV-Vic (N=214)	TIV-Yam+TIV-Vic(N=434)	QIV (N=449)	TIV-Yam (N=227)	TIV-Vic (N=221)	TIV-Yam+TIV-Vic(N=448)
A/California/7/2009												
GMT Value(95%CI)	485.33(444.13-530.36)	371.24(329.37-418.44)	491.88(435.18-555.96)	427.12(391.95-465.45)	332.23(300.26-367.60)	206.52(174.77-244.03)	394.99(336.49-463.65)	284.33(252.35-320.36)	183.56(159.33-211.49)	154.72(128.87-185.74)	255.32(207.57-314.04)	198.08(172.33-227.69)
SCR%(95%CI)	87.82(85.49-89.90)	85.71(82.13-88.82)	88.54(85.21-91.35)	87.12(84.75-89.25)	91.29(88.20-93.80)	87.27(82.13-91.37)	92.06(87.59-95.30)	89.63(86.37-92.34)	84.19(80.48-87.44)	81.50(75.82-86.33)	86.43(81.19-90.65)	83.93(80.19-87.21)
SPR%(95%CI)	94.93(93.27-96.28)	95.09(92.66-96.90)	96.85(94.78-98.27)	95.97(94.46-97.16)	97.88(96.02-99.03)	95.00(91.23-97.48)	98.13(95.28-99.49)	96.54(94.36-98.05)	88.42(85.09-91.23)	87.67(82.67-91.64)	88.69(83.76-92.54)	88.17(84.81-91.01)
GMFI Value(95%CI)	24.04(21.78-26.53)	18.31(16.02-20.92)	23.99(20.89-27.54)	20.95(19.02-23.06)	26.79(23.54-30.48)	18.26(15.17-21.99)	33.05(26.97-40.51)	24.47(21.28-28.14)	20.77(18.02-23.94)	16.05(13.36-19.28)	28.67(23.49-35.01)	21.37(18.62-24.52)
A/Switzerland/9715293/2013												
GMT Value(95%CI)	471.13(436.75-508.22)	426.05(383.91-472.82)	434.25(389.22-484.48)	430.12(398.88-463.80)	237.04(215.28-261.00)	245.59(208.65-289.07)	273.04(234.61-317.76)	258.76(231.55-289.17)	462.79(413.65-517.77)	493.70(415.35-586.82)	470.64(394.20-561.91)	482.19(426.26-545.45)
SCR%(95%CI)	75.65(72.68-78.44)	73.21(68.86-77.26)	70.56(66.09-74.76)	71.89(68.82-74.82)	83.29(79.40-86.72)	80.45(74.59-85.48)	82.24(76.45-87.12)	81.34(77.35-84.89)	88.20(84.85-91.03)	86.34(81.18-90.53)	85.07(79.67-89.49)	85.71(82.13-88.82)
SPR%(95%CI)	99.32(98.53-99.75)	100.00(99.18-100)	99.78(98.75-99.99)	99.89(99.38-100.00)	98.35(96.64-99.34)	95.91(92.38-98.11)	99.07(96.66-99.89)	97.47(95.51-98.73)	99.11(97.73-99.76)	98.68(96.19-99.73)	98.64(96.08-99.72)	98.66(97.11-99.51)
GMFI Value (95%CI)	9.22(8.42-10.08)	7.91(6.95-9.01)	7.35(6.47-8.36)	7.63(6.97-8.36)	10.35(9.64-12.21)	11.46(9.55-13.74)	12.43(10.24-15.09)	11.93(10.45-13.61)	14.79(12.99-16.83)	15.33(12.66-18.56)	13.98(11.58-16.88)	14.65(12.81-16.75)
B/Brisbane/60/2008												
GMT Value(95%CI)	82.86(75.67-90.74)	10.85(10.01-11.77)	62.55(55.12-70.97)	-	61.13(55.05-67.87)	17.52(14.99-20.48)	44.22(38.47-50.84)	-	64.75(58.16-72.08)	18.59(15.96-21.64)	48.28(41.40-56.31)	-
SCR%(95%CI)	74.41(71.40-77.25)	4.69(2.92-7.08)	67.64(63.07-71.97)	-	70.35(65.76-74.66)	17.73(12.92-23.43)	59.35(52.44-65.99)	-	70.38(65.92-74.57)	19.82(14.84-25.61)	54.30(47.48-61.00)	-
SPR%(95%CI)	78.58(75.73-81.24)	14.06(10.98-17.63)	71.01(66.55-75.19)	-	76.47(72.14-80.42)	28.18(22.34-34.62)	64.49(57.67-70.89)	-	75.50(71.25-79.41)	29.96(24.07-36.37)	64.25(57.55-70.57)	-
GMFI Value (95%CI)	11.01(10.06-12.06)	1.42(1.34-1.49)	8.24(7.25-9.37)	-	7.90(7.09-8.79)	2.14(1.89-2.43)	5.92(5.14-6.81)	-	7.56(6.80-8.40)	2.17(1.91-2.46)	7.40(6.71-8.17)	-

B/Phuket/3073/2013												
GMT Value(95%CI)	179.62(167.32-192.82)	174.48(158.26-192.36)	45.17(41.48-49.18)	-	149.65(135.95-164.73))	105.23(91.42-121.12)	80.48(67.77-105.26)	-	181.03(163.60-200.33)	126.48(109.10-146.62)	87.89(74.40-103.84)	-
SCR%(95%CI)	83.54(80.93-85.92)	78.35(74.24-82.08)	29.66(25.45-34.14)	-	81.65(77.63-85.21)	67.27(60.64-73.43)	57.01(50.08-63.74)	-	84.41(80.72-87.64)	69.30(63.17-75.52)	55.66(48.84-62.32)	-
SPR%(95%CI)	94.02(92.26-95.49)	94.64(92.13-96.54)	67.42(62.84-71.75)	-	95.29(92.83-97.10)	88.18(83.16-92.13)	84.58(79.03-89.14)	-	95.77(93.47-97.43)	91.63(87.24-94.89)	81.45(75.69-86.35)	-
GMFI Value (95%CI)	10.00(9.26-10.80)	8.81(7.85-9.88)	2.50(2.32-2.68)	-	7.59(6.88-8.38)	5.31(4.62-6.11)	4.42(3.81-5.13)	-	8.05(7.26-8.92)	5.91(5.06-6.91)	3.95(3.42-4.57)	-

Abbreviations: CI, confidence interval; GMT, geometric mean titer; QIV, quadrivalent influenza vaccine; GMFI, geometric mean fold increases (defined as the geometric mean of the within-subjects ratios of the post-vaccination reciprocal HI titer to the day 0 reciprocal HI titer); SCR, seroconversion rate (defined as the proportion of vaccines with either a pre-vaccination titer <1:10 and a post-vaccination titer ⩾1:40, or a pre-vaccination titer ⩾1:10 and at least a 4-fold increase in post-vaccination titer); SPR, seroprotection rate (defined as the percentage of subjects who had a serumanti-HI antibody titer ⩾1:40); TIV-Vic, trivalent influenza vaccine Victoria lineage B strain; TIV-Yam, trivalent influenza vaccine Yamagata lineage B strain.

Table 3. Immunogenic non-inferiority comparison of QIV to TIV-Yam and TIV-Vic.

Age Group	Antibody type	TIV-Vic + TIV-Yam N(GMT, 95%CI)	QIV N (GMT, 95%CI)	GMT ratio GMT ratio (95% CI)[a]	Conclusion
Age 3-17 years	A/California/7/2009	893 (427.12,391.95-465.45)	887 (485.33,444.13-530.36)	0.88(0.78-1.00)[b]	noninferior
	A/Switzerland/9715293/2013	593(430.12,398.88-463.80)	887 (471.13,436.75-508.22)	0.91(0.82-1.02)[b]	noninferior
		TIV-Vic N(GMT, 95%CI)	QIV N (GMT, 95%CI)	GMT ratio GMT ratio (95% CI)[a]	
	B/Brisbane/60/2008	445(62.55,55.12-70.97)	887(82.86,75.67-90.74)	0.75(0.64-0.88)[c]	noninferior
	B/Phuket/3073/2013	445(45.17,41.48-49.18)	887 (179.62,167.32-192.82)	0.25(0.23-0.28)[c]	superior
		TIV-Yam N(GMT, 95%CI)	QIV N (GMT, 95%CI)	GMT ratio GMT ratio (95% CI)[a]	
	B/Brisbane/60/2008	448(10.85,10.01-11.77)	887(82.86,75.67-90.74)	0.13(0.11-0.15)[d]	superior
	B/Phuket/3073/2013	448(174.48,158.26-192.36)	887 (179.62,167.32-192.82)	0.97(0.86-1.10)[d]	noninferior
		TIV-Vic + TIV-Yam N(GMT, 95%CI)	QIV N (GMT, 95%CI)	GMT ratio GMT ratio (95% CI)[a]	
Age 18-59 years	A/California/7/2009	434(284.33,252.35-320.36)	425(332.23,300.26-367.60)	0.86(0.73-1.00)[b]	noninferior
	A/Switzerland/9715293/2013	434(258.76,231.55-289.17)	425(237.04,215.28-261.00)	1.09(0.94-1.26)[b]	noninferior

		TIV-Vic	QIV	GMT ratio	
		N(GMT, 95%CI)	N (GMT, 95%CI)	GMT ratio (95% CI)[a]	
	B/Brisbane/60/2008	214(44.22,38.47-50.84)	425(61.13,55.05-67.87)	0.72(0.61-0.86)[c]	noninferior
	B/Phuket/3073/2013	214(80.48,67.77-105.26)	425 (149.65,135.95-164.73)	0.53(0.41-0.52)[c]	superior
		TIV-Yam	QIV	GMT ratio	
		N(GMT, 95%CI)	N (GMT, 95%CI)	GMT ratio (95% CI)[a]	
	B/Brisbane/60/2008	220(17.52,14.99-20.48)	425(61.13,55.05-67.87)	0.29(0.24-0.35)[d]	superior
	B/Phuket/3073/2013	220(105.23,91.42-121.12)	425 (149.65,135.95-164.73)	0.70(0.59-0.83)[d]	noninferior
		TIV-Vic + TIV-Yam	QIV	GMT ratio	
		N(GMT, 95%CI)	N (GMT, 95%CI)	GMT ratio (95% CI)[a]	
Elderly above 60 years	A/California/7/2009	448(198.08, 172.33-227.69)	449(183.56, 159.33-211.49)	1.08(0.88-1.32)[b]	noninferior
	A/Switzerland/9715293/2013	448(482.19, 426.26-545.45)	449(462.79, 413.65-517.77)	1.04(0.88-1.23)[b]	noninferior
		TIV-Vic	QIV	GMT ratio	
		N(GMT, 95%CI)	N (GMT, 95%CI)	GMT ratio (95% CI)[a]	
	B/Brisbane/60/2008	221(48.28, 41.40-56.31)	449(64.75, 58.16-72.08)	0.75(0.62-0.9)[c]	noninferior
	B/Phuket/3073/2013	221(87.89, 74.40-103.84)	449(181.03, 163.60-200.33)	0.49(0.4-0.58)[c]	superior
		TIV-Yam	QIV	GMT ratio	
		N(GMT, 95%CI)	N (GMT, 95%CI)	GMT ratio (95% CI)[a]	
	B/Brisbane/60/2008	227 (18.59, 15.96-21.64)	449(64.75, 58.16-72.08)	0.29(0.24-0.35)[d]	superior
	B/Phuket/3073/2013	227(126.48, 109.10-146.62)	449(181.03, 163.60-200.33)	0.70(0.59-0.83)[d]	noninferior
		TIV-Vic + TIV-Yam	QIV n/N	SCR difference%	
		n/N seroconverted (SCR)	seroconverted (SCR)	difference (95% CI)[a]	
Age 3-17 years	A/California/7/2009	778/893 (87.12)	779/887(87.82)	-0.70(-3.78-2.37)[f]	noninferior
	A/Switzerland/9715293/2013	642/893 (71.89)	671/887 (75.65)	-3.76(-7.84-0.33)[f]	noninferior
		TIV-Vic	QIV n/N	SCR difference%	
		n/N seroconverted (SCR)	seroconverted (SCR)	difference (95% CI)[a]	
	B/Brisbane/60/2008	301/445(67.64)	660/887 (74.41)	-6.77(-11.98--1.56)[g]	noninferior
	B/Phuket/3073/2013	132/445 (29.66)	741/887 (83.54)	-53.88(-58.77--48.98)[g]	superior
		TIV-Yam	QIV n/N	SCR difference%	
		n/N seroconverted (SCR)	seroconverted (SCR)	difference (95% CI)[a]	
	B/Brisbane/60/2008	21/448(4.69)	660/887 (74.41)	-69.72(-73.20--66.25)[h]	superior
	B/Phuket/3073/2013	351/448(78.35)	1088/887 (83.54)	-5.19(-9.72--0.66)[h]	noninferior
		TIV-Vic + TIV-Yam	QIV n/N	SCR difference%	

		n/N seroconverted (SCR)	seroconverted (SCR)	difference (95% CI)[a]	
Age 18-59 years	A/California/7/2009	399/434(89.63)	388/425(91.29)	-1.66(-5.59-2.26)[f]	noninferior
	A/Switzerland/9715293/2013	353/434 (81.34)	354/425 (83.29)	-1.96(-7.06-3.14)[f]	noninferior
		TIV-Vic	QIV n/N	SCR difference%	
		n/N seroconverted (SCR)	seroconverted (SCR)	difference (95% CI)[a]	
	B/Brisbane/60/2008	127/214(59.35)	299/425 (70.35)	-11.01(-18.89--3.12)[g]	noninferior
	B/Phuket/3073/2013	122/214 (57.01)	347/425 (81.65)	-24.64(-32.22--17.05)[g]	superior
		TIV-Yam	QIV n/N	SCR difference%	
		n/N seroconverted (SCR)	seroconverted (SCR)	difference (95% CI)[a]	
	B/Brisbane/60/2008	39/220(17.73)	299/425 (70.35)	-52.63(-59.28--45.97)[h]	superior
	B/Phuket/3073/2013	148/220 (67.27)	347/425 (81.65)	-14.37(-21.58--7.16)[h]	noninferior
		TIV-Vic + TIV-Yam	QIV n/N	SCR difference%	
		n/N seroconverted (SCR)	seroconverted (SCR)	difference (95% CI)[a]	
Elderly above 60 years	A/California/7/2009	376/448(83.93)	378/449(84.19)	-0.26(-5.05-4.53)[f]	noninferior
	A/Switzerland/9715293/2013	384/448(85.71)	396/449(88.20)	-2.48(-6.89-1.92)[f]	noninferior
		TIV-Vic	QIV n/N	SCR difference%	
		n/N seroconverted (SCR)	seroconverted (SCR)	difference (95% CI)[a]	
	B/Brisbane/60/2008	120/221(54.30)	316/449(70.38)	-16.08(-23.89--8.27)[g]	noninferior
	B/Phuket/3073/2013	123/221(55.66)	379/449(84.41)	-28.75(-36.11--21.39)[g]	superior
		TIV-Yam	QIV n/N	SCR difference%	
		n/N seroconverted (SCR)	seroconverted (SCR)	difference (95% CI)[a]	
	B/Brisbane/60/2008	45/227(19.82)	316/449(70.38)	-50.55(-57.24--43.87)[h]	superior
	B/Phuket/3073/2013	158/227(69.60)	379/449(84.41)	-14.81(-21.67--7.95)[h]	noninferior

Abbreviations: CI, confidence interval; GMT, geometric mean titer; N, number: QIV, quadrivalent influenza vaccine ; SCR, seroconversionrate; TIV-Vic, trivalent influenza vaccine Victoria lineage B strain; TIV-Yam, trivalent influenza vaccine Yamagata lineage B strain.

[a] Immunogenic noninferiority demonstrated if the upper limit of the 2-sided 95% CI of GMT was ≤1.5 and the upper limit of the 2-sided 95% CI of the difference between SCR was ≤10% for all vaccine strains. Immunogenic.superiority demonstrated if the upper limit of the 2-side d 95% CI of GMT did not exceed 2/3 and the upper limit of the 2-sided 95% CI of the difference between SCRs did not exceed -10% with respect to each B strain in the QIV compared with corresponding TIV lacking the same B strain .

[b] (TIV-V ic + TIV-Yam) divided by QIV.

[c] TIV-Vic divided by QIV.

[d] TIV-Yam divided by QIV.

[e] SCR was defined as the proportion of vaccinees with either a prevaccination titer <1:10 and a postvaccination titer ≥1:40, or a prevaccination titer ≥ 1:10 and at least a 4-fold increase in postvaccination titer.

[f] (TIV-Vi c + TIV- Yam) minus QIV.

[g] TIV-Vic minus QIV.

[h] TIV-Yam minus QIV.

Table 4. Summary of serious adverse event and adverse reactions

		QIV			TIV-Yam			TIV-Vic			
		n(N=913)	%	95%CI	n(N=458)	%	95% CI	n(N=458)	%	95% CI	p value
Age 3-17 years											
SAEs											
SAEs within 6 m after vaccination		4	0.44	0.12-1.12	1	0.22	0.01-1.21	1	0.22	0.01-1.21	0.7650
Overall adverse reactions											
	Any	178	19.50	16.97-22.22	88	19.21	15.71-23.13	91	19.87	16.31-23.82	0.9689
	Grade 3	5	0.55	0.18-1.27	1	0.22	0.01-1.21	1	0.22	0.01-1.21	0.6916
Injection-site adverse reactions											
	Any	38	4.16	2.96-5.67	11	2.40	1.20-4.26	19	4.15	2.52-6.40	0.2280
	Grade 3	1	0.11	0.00-0.61	0	0.00	0.00-0.80	0	0.00	0.00-0.80	0.6054
Induration	Any	5	0.55	0.18-1.27	0	0.00	0.00-0.80	2	0.44	0.05-1.57	0.3695
	Grade 3	0	0.00	0.00-0.40	0	0.00	0.00-0.80	0	0.00	0.00-0.80	-
Redness	Any	1	0.11	0.00-0.61	0	0.00	0.00-0.80	1	0.22	0.01-1.21	1.0000
	Grade 3	0	0.00	0.00-0.40	0	0.00	0.00-0.80	0	0.00	0.00-0.80	-
Pain	Any	32	3.50	2.41-4.91	10	2.18	1.05-3.98	16	3.49	2.01-5.61	0.3788
	Grade 3	1	0.11	0.00-0.61	0	0.00	0.00-0.80	0	0.00	0.00-0.80	1.0000
Swelling	Any	5	0.55	0.55	1	0.22	0.01-1.21	1	0.22	0.01-1.21	0.6916
	Grade 3	0	0.00	0.00-0.40	0	0.00	0.00-0.80	0	0.00	0.00-0.80	-
Itch	Any	1	0.11	0.00-0.61	0	0.00	0.00-0.80	1	0.22	0.01-1.21	1.0000
	Grade 3	0	0.00	0.00-0.40	0	0.00	0.00-0.80	0	0.00	0.00-0.80	-
Systemic adverse reactions											
	Any	153	16.76	14.39-19.34	79	17.25	13.90-21.03	80	17.47	14.10-21.26	0.9398
	Grade 3	4	0.44	0.12-1.12	1	0.22	0.01-1.21	1	0.22	0.01-1.21	0.7650
Fever	Any	143	15.66	13.36-18.19	72	15.72	12.51-19.38	75	16.38	13.10-20.09	0.9396
	Grade 3	4	0.44	0.12-1.12	1	0.22	0.01-1.21	1	0.22	0.01-1.21	0.7650
Diarrhea	Any	3	0.33	0.07-0.96	2	0.44	0.05-1.57	2	0.44	0.05-1.57	0.9323
	Grade 3	0	0.00	0.00-0.40	0	0.00	0.00-0.80	0	0.00	0.00-0.80	-
Cough	Any	8	0.88	0.38-1.72	8	1.75	0.76-3.41	4	0.87	0.24-2.22	0.2996

	Grade 3	0	0.00	0.00-0.40	0	0.00	0.00-0.80	0	0.00	0.00-0.80	-
Nausea/Vomiting	Any	2	0.22	0.03-0.79	1	0.22	0.01-1.21	4	0.87	0.24-2.22	0.1659
	Grade 3	0	0.00	0.00-0.40	0	0.00	0.00-0.80	0	0.00	0.00-0.80	-
Fatigue	Any	3	0.33	0.07-0.96	2	0.44	0.05-1.57	2	0.44	0.05-1.57	0.1252
	Grade 3	0	0.00	0.00-0.40	0	0.00	0.00-0.80	0	0.00	0.00-0.80	-
Muscle pain	Any	8	0.88	0.38-1.72	1	0.22	0.01-1.21	0	0.00	0.00-0.80	0.0677
	Grade 3	0	0.00	0.00-0.40	0	0.00	0.00-0.80	0	0.00	0.00-0.80	-
Headache	Any	7	0.77	0.31-1.57	3	0.66	0.14-1.90	2	0.44	0.05-1.57	0.9290
	Grade 3	0	0.00	0.00-0.40	0	0.00	0.00-0.80	0	0.00	0.00-0.80	-
Non-solicited adverse reactions											
	Any	36	3.94	2.78-5.42	15	3.28	1.84-5.34	17	3.71	2.18-5.88	0.8269
	Grade 3	3	0.33	0.07-0.96	1	0.22	0.01-1.21	1	0.22	0.01-1.21	1.0000
		n(N=459)	%	95%CI	n(N=229)	%	95% CI	n(N=231)	%	95% CI	p value
Age 18-59 years											
SAEs											
SAEs within 6 m after vaccination		5	1.09	0.35-2.52	5	2.18	0.71-5.02	1	0.43	0.01-2.39	0.2463
Overall adverse reactions											
	Any	61	13.29	10.32-16.74	26	11.35	7.55-16.19	40	17.32	12.67-22.82	0.1613
	Grade 3	0	0.00	0.00-0.80	0	0.00	0.00-1.60	0	0.00	0.00-1.58	-
Injection-site adverse reactions											
	Any	21	4.58	2.85-6.91	9	3.93	1.81-7.33	19	8.23	5.02-12.55	0.0727
	Grade 3	0	0.00	0.00-0.80	0	0.00	0.00-1.60	0	0.00	0.00-1.58	-
Induration	Any	2	0.44	0.05-1.57	0	0.00	0.00-1.60	2	0.87	0.11-3.09	0.5622
	Grade 3	0	0.00	0.00-0.80	0	0.00	0.00-1.60	0	0.00	0.00-1.58	-
Redness	Any	1	0.07	0.00-0.41	0	0.00	0.00-0.54	1	0.15	0.00-0.81	1.0000
	Grade 3	0	0.00	0.00-0.80	0	0.00	0.00-1.60	0	0.00	0.00-1.58	-
Pain	Any	17	3.70	2.17-5.86	8	3.49	1.52-6.77	19	8.23	5.02-12.55	**0.0182**[a]

	Grade 3	0	0.00	0.00-0.80	0	0.00	0.00-1.60	0	0.00	0.00-1.58	-
Swelling	Any	4	0.87	0.24-2.22	1	0.44	0.01-2.41	0	0.00	0.00-1.58	
	Grade 3	0	0.00	0.00-0.80	0	0.00	0.00-1.60	0	0.00	0.00-1.58	-
Itch	Any	1	0.22	0.01-1.21	1	0.44	0.01-2.41	0	0.00	0.00-1.58	0.7486
	Grade 3	0	0.00	0.00-0.80	0	0.00	0.00-1.60	0	0.00	0.00-1.58	-
Systemic adverse reactions											
	Any	44	9.59	7.05-12.65	18	7.86	4.72-12.14	26	11.26	7.49-16.06	0.4651
	Grade 3	0	0.00	0.00-0.80	0	0.00	0.00-1.60	0	0.00	0.00-1.58	-
Fever	Any	35	7.63	5.37-10.45	15	6.55	3.71-10.57	21	9.09	5.72-13.56	0.5903
	Grade 3	0	0.00	0.00-0.80	0	0.00	0.00-1.60	0	0.00	0.00-1.58	-
Diarrhea	Any	4	0.29	0.08-0.74	3	0.44	0.09-1.27	3	0.44	0.09-1.27	0.7688
	Grade 3	0	0.00	0.00-0.80	0	0.00	0.00-1.60	0	0.00	0.00-1.58	-
Cough	Any	4	0.87	0.24-2.22	0	0.00	0.00-1.60	5	2.16	0.71-4.98	**0.0498**[b]
	Grade 3	0	0.00	0.00-0.80	0	0.00	0.00-1.60	0	0.00	0.00-1.58	-
Nausea/Vomiting	Any	2	0.44	0.05-1.57	0	0.00	0.00-1.60	0	0.00	0.00-1.58	0.7486
	Grade 3	0	0.00	0.00-0.80	0	0.00	0.00-1.60	0	0.00	0.00-1.58	-
Fatigue	Any	2	0.44	0.05-1.57	3	1.31	0.27-3.78	2	0.87	0.11-3.09	0.4196
	Grade 3	0	0.00	0.00-0.80	0	0.00	0.00-1.60	0	0.00	0.00-1.58	-
Muscle pain	Any	1	0.22	0.01-1.21	2	0.87	0.11-3.12	0	0.00	0.00-1.58	0.2179
	Grade 3	0	0.00	0.00-0.80	0	0.00	0.00-1.60	0	0.00	0.00-1.58	-
Headache	Any	3	0.65	0.13-1.90	2	0.87	0.11-3.12	2	0.87	0.11-3.09	1.0000
	Grade 3	0	0.00	0.00-0.80	0	0.00	0.00-1.60	0	0.00	0.00-1.58	-
Non-solicited adverse reactions											
	Any	34	7.41	5.18-10.20	12	5.24	2.74-8.97	15	6.49	3.68-10.48	0.5576
	Grade 3	1	0.22	0.01-1.21	0	0.00	0.00-1.60	0	0.00	0.00-1.58	1.0000
		n(N=457)	%	95%CI	n(N=229)	%	95% CI	n(N=227)	%	95% CI	p value
Elderly above 60 years											
SAEs											
SAEs within 6 m after vaccination		9	0.66	0.30-1.24	7	1.02	0.41-2.09	4	0.58	0.16-1.48	0.5739
Overall adverse reactions											
	Any	54	11.82	9.00-15.14	18	7.86	4.72-12.14	20	8.81	5.46-13.28	0.2050
	Grade 3	0	0.00	0.00-0.80	0	0.00	0.00-1.60	0	0.00	0.00-1.61	-
Injection-site adverse reactions											

	Any	23	5.03	3.22-7.46	8	3.49	1.52-6.77	9	3.96	1.83-7.39	0.6102
	Grade 3	0	0.00	0.00-0.80	0	0.00	0.00-1.60	0	0.00	0.00-1.61	-
Induration	Any	1	0.22	0.01-1.21	0	0.00	0.00-1.60	0	0.00	0.00-1.61	1.0000
	Grade 3	0	0.00	0.00-0.80	0	0.00	0.00-1.60	0	0.00	0.00-1.61	-
Redness	Any	2	0.44	0.05-1.57	3	1.31	0.27-3.78	0	0.00	0.00-1.61	0.2364
	Grade 3	0	0.00	0.00-0.80	0	0.00	0.00-1.60	0	0.00	0.00-1.61	-
Pain	Any	18	3.94	2.35-6.15	5	2.18	0.71-5.02	9	3.96	1.83-7.39	0.4541
	Grade 3	0	0.00	0.00-0.80	0	0.00	0.00-1.60	0	0.00	0.00-1.61	-
Swelling	Any	9	0.66	0.30-1.24	2	0.29	0.04-1.05	1	0.15	0.00-0.81	0.1193
	Grade 3	0	0.00	0.00-0.80	0	0.00	0.00-1.60	0	0.00	0.00-1.61	-
Itch	Any	3	0.15	0.14-1.91	1	0.15	0.00-0.81	2	0.15	0.11-3.15	0.7638
	Grade 3	0	0.00	0.00-0.27	0	0.00	0.00-0.54	0	0.00	0.00-0.53	-
Systemic adverse reactions											
	Any	36	7.88	5.58-10.74	10	4.37	2.11-7.88	18	7.93	4.77-12.24	0.1943
	Grade 3	0	0.00	0.00-0.80	0	0.00	0.00-1.60	0	0.00	0.00-1.61	-
Fever	Any	27	5.91	3.93-8.48	4	1.75	0.48-4.41	16	7.05	4.08-11.19	**0.0219**[c]
	Grade 3	0	0.00	0.00-0.80	0	0.00	0.00-0.80	0	0.00	0.00-0.80	-
Diarrhea	Any	2	0.44	0.05-1.57	1	0.44	0.01-2.41	0	0.00	0.00-1.61	1.0000
	Grade 3	0	0.00	0.00-0.80	0	0.00	0.00-0.80	0	0.00	0.00-0.80	-
Cough	Any	6	1.31	0.48-2.84	2	0.87	0.11-3.12	3	1.32	0.27-3.81	0.8571
	Grade 3	0	0.00	0.00-0.80	0	0.00	0.00-0.80	0	0.00	0.00-0.80	-
Nausea/Vomiting	Any	0	0.00	0.00-0.80	0	0.00	0.00-0.80	0	0.00	0.00-0.80	-
	Grade 3	0	0.00	0.00-0.80	0	0.00	0.00-0.80	0	0.00	0.00-0.80	-
Fatigue	Any	4	0.88	0.24-2.23	2	0.87	0.11-3.12	2	0.88	0.11-3.15	1.0000
	Grade 3	0	0.00	0.00-0.80	0	0.00	0.00-0.80	0	0.00	0.00-0.80	-
Muscle pain	Any	1	0.22	0.01-1.21	0	0.00	0.00-0.80	0	0.00	0.00-0.80	1.0000
	Grade 3	0	0.00	0.00-0.80	0	0.00	0.00-0.80	0	0.00	0.00-0.80	-
Headache	Any	3	0.66	0.14-1.91	2	0.87	0.11-3.12	1	0.44	0.01-2.43	1.0000
	Grade 3	0	0.00	0.00-0.80	0	0.00	0.00-0.80	0	0.00	0.00-0.80	-
Non-solicited adverse reactions											
	Any	39	8.53	6.14-11.48	19	8.30	5.07-12.65	29	12.78	8.73-17.83	0.1570
	Grade 3	1	0.22	0.01-1.21	1	0.44	0.01-2.41	0	0.00	0.00-1.61	1.0000

Abbreviations: N, number of participants in the total vaccinated cohort for safety. n, number of participants with the corresponding adverse reaction.%, incidence of the corresponding adverse

reaction percent.

[a] post Hoc Multiple Comparision shows the incidence of pain reactions within participants 18-59 years of age was significantly higher in TIV-Vic group than QIV and TIV-Yam group

[b] post Hoc Multiple Comparision shows the incidence of cough reactions within participants 18-59 years of age was significantly lower in TIV-Yam group than TIV-Vic group

[c] post Hoc Multiple Comparision shows the incidence of fever reactions within elderly above 60 years was significantly lower in TIV-Vic group than QIV and TIV-Yam group

Appendix 1. Full list of the inclusion and exclusion criteria

Inclusion criteria
1. Healthy volunteers over 3 years old
2. Based on medical history and physical examination, subject is eligible for vaccination
3. Subjects(or/and the subjects' guardian)were able to agree with the informed consent and signed it
4. Participants were able to comply with the requirements of the program
5. Axillary temperature≤37.0℃
Exclusion criteria
1. With medical history or family medical history of allergies, convulsions, seizures, encephalopathy, or psychosis
2. Vaccinated against influenza in the past 6 months
3. Allergic to any component of the vaccine
4. For female above18 years of age, if The urine pregnancy test was positive, pregnant or lactating
5. Immune dysfunction
6. In the past 6 months have been suffering from seasonal influenza
7. With fever or infectious disease
8. Suffering from congenital malformations, developmental disabilities or serious chronic diseases
9. With thrombocytopenia or other coagulation disorders
10. Received immunosuppressive therapy, anti-allergic therapy, cytotoxic therapy, inhaled corticosteroids In the past 6 months
11. Received any subunit vaccine or inactivated vaccines in the last 14 days
12. Received any experiment drug in the last 30 days
13. Received any live attenuated vaccine in the last 30 days

Appendix 2. Reasons for participants who were assessed but not enrolled

Reason for not enrolled	No. of participants
Subjects(or/and the subjects' guardian) refused to sign the informed consent	81
Based on medical history and physical examination, subject is not eligible for vaccination	18
Axillary temperature>37.0℃	152
With medical history or family medical history of allergies, convulsions, seizures, encephalopathy	55
With infectious disease	21
Vaccinated against influenza in the past 6 months	8
The urine pregnancy test was positive	1
In the past 6 months have been suffering from seasonal influenza	12
Suffering from congenital malformations, developmental disabilities or serious chronic diseases	52
Received immunosuppressive therapy, anti-allergic therapy, cytotoxic therapy, inhaled corticosteroids In the past 6 months	5
Received any subunit vaccine or inactivated vaccines in the last 14 days	2
Total	405

Appendix 3: List of grade 3 solicited injection-site and systematic adverse reactions reported during the follow-up

ID of participant	Treatment group	Symptom	On set time
112	TIV-Vic	Fever	7 days after the injections
192	TIV-Yam	Fever	3 days after the injection
566	QIV	Fever	Within 24 hours after the injections
670	QIV	Fever	6 days after the injections
743	QIV	Fever	Within 24 hours after the injections
1097	QIV	Fever	4 days after the injection
242	QIV	Pain	Within 24 hours after the injections

Appendix 4. List of reported serious adverse events during the study

Group		No. of cases
QIV group		
	Infections and infestations	1
	Skin and subcutaneous tissue disorders	1
	Gastrointestinal disorders	2

	Renal and urinary disorders	3
	Respiratory system/chest/mediastinal disorders	0
	Reproductive system and breast disorders	3
	Neurological disorders	4
	Circulation system disease	4
	Hepatobiliary disease	0
	Musculoskeletal diseases	0
	Surgical and medical procedures	0
TIV-Vic group		
	Infections and infestations	4
	Skin and subcutaneous tissue disorders	0
	Gastrointestinal disorders	0
	Renal and urinary disorders	2
	Respiratory system/chest/mediastinal disorders	1
	Reproductive system and breast disorders	1
	Neurological disorders	2
	Circulation system disease	0
	Hepatobiliary disease	1
	Musculoskeletal diseases	1
	Surgical and medical procedures	1
TIV-Vic group		
	Infections and infestations	0
	Skin and subcutaneous tissue disorders	0
	Gastrointestinal disorders	1
	Renal and urinary disorders	1
	Respiratory system/chest/mediastinal disorders	1
	Reproductive system and breast disorders	0
	Neurological disorders	2
	Circulation system disease	0
	Hepatobiliary disease	0
	Musculoskeletal diseases	1
	Surgical and medical procedures	0
Total		37

Appendix 5. Summary of serious adverse event and adverse reactions for subgroups

		QIV			TIV-Yam			TIV-Vic			
		n(N=460)	%	95%CI	n(N=230)	%	95% CI	n(N=229)	%	95% CI	p value
Age 3-9 years											
SAEs		4	0.87	0.24-2.21	1	0.43	0.01-2.40	0	0.00	0.00-1.60	0.5292
SAEs within 6 m after vaccination											
Overall adverse reactions											
	Any	80	17.39	14.04-21.17	39	16.96	12.34-22.44	42	18.34	13.55-23.97	0.9219
	Grade 3	4	0.87	0.24-2.21	1	0.43	0.01-2.40	1	0.44	0.01-2.41	0.8819
Injection-site adverse reactions											
	Any	16	3.48	2.00-5.59	5	2.17	0.71-5.00	8	3.49	1.52-6.77	0.6165
	Grade 3	1	0.22	0.01-1.21	0	0.00	0.00-1.59	0	0.00	0.00-1.60	1.0000
Induration	Any	3	0.65	0.13-1.89	0	0.00	0.00-1.59	1	0.44	0.01-2.41	0.6861
	Grade 3	0	0.00	0.00-0.80	0	0.00	0.00-1.59	0	0.00	0.00-1.60	-
Redness	Any	1	0.22	0.01-1.21	0	0.00	0.00-1.59	1	0.44	0.01-2.41	0.4989
	Grade 3	0	0.00	0.00-0.80	0	0.00	0.00-1.59	0	0.00	0.00-1.60	-
Pain	Any	11	2.39	1.20-4.24	5	2.17	0.71-5.00	6	2.62	0.97-5.62	0.9523
	Grade 3	1	0.22	0.01-1.21	0	0.00	0.00-0.81	0	0.00	0.00-1.60	1.0000
Swelling	Any	2	0.43	0.05-1.56	0	0.00	0.00-1.59	1	0.44	0.01-2.41	0.6238
	Grade 3	0	0.00	0.00-0.80	0	0.00	0.00-1.59	0	0.00	0.00-1.60	-
Itch	Any	1	0.22	0.01-1.21	0	0.00	0.00-0.81	0	0.00	0.00-1.60	1.0000
	Grade 3	0	0.00	0.00-0.80	0	0.00	0.00-1.59	0	0.00	0.00-1.60	-
Systemic adverse reactions											
	Any	71	15.43	12.26-19.07	35	15.22	10.83-20.52	38	16.59	12.02-22.06	0.9036
	Grade 3	3	0.65	0.13-1.89	1	0.43	0.01-2.40	1	0.44	0.01-2.41	1.0000
Fever	Any	70	15.22	12.06-18.83	31	13.48	9.34-18.58	35	15.28	10.88-20.61	0.8087
	Grade 3	3	0.65	0.13-1.89	1	0.43	0.01-2.40	1	0.44	0.01-2.41	1.0000
Diarrhea	Any	0	0.00	0.00-0.80	1	0.43	0.01-2.40	1	0.44	0.01-2.41	0.2492
	Grade 3	0	0.00	0.00-0.80	0	0.00	0.00-1.59	0	0.00	0.00-1.60	-
Cough	Any	4	0.87	0.24-2.21	6	2.61	0.96-5.59	4	1.75	0.48-4.41	0.1807
	Grade 3	0	0.00	0.00-0.80	0	0.00	0.00-1.59	0	0.00	0.00-1.60	-

Nausea/Vomiting	Any	1	0.22	0.01-1.21	0	0.00	0.00-1.59	2	0.87	0.11-3.12	0.2173
	Grade 3	0	0.00	0.00-0.80	0	0.00	0.00-1.59	0	0.00	0.00-1.60	-
Fatigue	Any	0	0.00	0.00-0.80	0	0.00	0.00-1.59	2	0.87	0.11-3.12	0.0619
	Grade 3	0	0.00	0.00-0.80	0	0.00	0.00-1.59	0	0.00	0.00-1.60	-
Muscle pain	Any	2	0.43	0.05-1.56	0	0.00	0.00-1.59	0	0.00	0.00-1.60	0.7492
	Grade 3	0	0.00	0.00-0.80	0	0.00	0.00-1.59	0	0.00	0.00-1.60	-
Headache	Any	1	0.22	0.01-1.21	0	0.00	0.00-1.59	0	0.00	0.00-1.60	1.0000
	Grade 3	0	0.00	0.00-0.80	0	0.00	0.00-1.59	0	0.00	0.00-1.60	-
Non-solicited adverse reactions											
	Any	25	5.43	3.55-7.92	9	3.91	1.80-7.30	14	6.11	3.38-10.04	0.5472
	Grade 3	3	0.65	0.13-1.89	1	0.43	0.01-2.40	1	0.44	0.01-2.41	1.0000
		n(N=453)	%	95%CI	n(N=228)	%	95% CI	n(N=229)	%	95% CI	p value
Age 10-17 years											
SAEs											
SAEs within 6 m after vaccination		0	0.00	0.00-0.81	0	0.00	0.00-1.60	1	0.44	0.01-2.41	0.5022
Overall adverse reactions											
	Any	98	21.63	17.93-25.71	49	21.49	16.34-27.40	49	21.40	16.27-27.28	0.9973
	Grade 3	1	0.22	0.01-1.22	0	0.00	0.00-1.60	0	0.00	0.00-1.60	1.0000
Injection-site adverse reactions											
	Any	22	4.86	3.07-7.26	6	2.63	0.97-5.64	11	4.80	2.42-8.43	0.3624
	Grade 3	0	0.00	0.00-0.81	0	0.00	0.00-1.60	0	0.00	0.00-1.60	-
Induration	Any	2	0.44	0.05-1.59	0	0.00	0.00-1.60	1	0.44	0.01-2.41	0.8111
	Grade 3	0	0.00	0.00-0.81	0	0.00	0.00-1.60	0	0.00	0.00-1.60	-
Redness	Any	0	0.00	0.00-0.81	0	0.00	0.00-1.60	0	0.00	0.00-1.60	-
	Grade 3	0	0.00	0.00-0.81	0	0.00	0.00-1.60	0	0.00	0.00-1.60	-
Pain	Any	21	4.64	2.89-7.00	5	2.19	0.72-5.04	10	4.37	2.11-7.88	0.2840
	Grade 3	0	0.00	0.00-0.81	0	0.00	0.00-1.60	0	0.00	0.00-1.60	-
Swelling	Any	3	0.66	0.14-1.92	1	0.44	0.01-2.42	0	0.00	0.00-1.60	0.6875
	Grade 3	0	0.00	0.00-0.81	0	0.00	0.00-1.60	0	0.00	0.00-1.60	-
Itch	Any	0	0.00	0.00-0.81	0	0.00	0.00-1.60	1	0.44	0.01-2.41	0.5022
	Grade 3	0	0.00	0.00-0.81	0	0.00	0.00-1.60	0	0.00	0.00-1.60	-
Systemic adverse reactions											
	Any	82	18.10	14.66-21.96	44	19.30	14.39-25.03	42	18.34	13.55-23.97	0.9290

	Grade 3	1	0.22	0.01-1.22	0	0.00	0.00-1.60	0	0.00	0.00-1.60	1.0000
Fever	Any	73	16.11	12.85-19.83	41	17.98	13.22-23.59	40	17.47	12.78-23.02	0.8022
	Grade 3	1	0.22	0.01-1.22	0	0.00	0.00-1.60	0	0.00	0.00-1.60	1.0000
Diarrhea	Any	3	0.66	0.14-1.92	1	0.44	0.01-2.42	1	0.44	0.01-2.41	1.0000
	Grade 3	0	0.00	0.00-0.81	0	0.00	0.00-1.60	0	0.00	0.00-1.60	-
Cough	Any	4	0.88	0.24-2.25	2	0.88	0.11-3.13	0	0.00	0.00-1.60	0.3820
	Grade 3	0	0.00	0.00-0.81	0	0.00	0.00-1.60	0	0.00	0.00-1.60	-
Nausea/Vomiting	Any	1	0.22	0.01-1.22	1	0.44	0.01-2.42	2	0.87	0.11-3.12	0.5639
	Grade 3	0	0.00	0.00-0.81	0	0.00	0.00-1.60	0	0.00	0.00-1.60	-
Fatigue	Any	3	0.66	0.14-1.92	2	0.88	0.11-3.13	0	0.00	0.00-1.60	0.5292
	Grade 3	0	0.00	0.00-0.81	0	0.00	0.00-1.60	0	0.00	0.00-1.60	-
Muscle pain	Any	6	1.32	0.49-2.86	1	0.44	0.01-2.42	0	0.00	0.00-1.60	0.1929
	Grade 3	0	0.00	0.00-0.81	0	0.00	0.00-1.60	0	0.00	0.00-1.60	-
Headache	Any	6	1.32	0.49-2.86	3	1.32	0.27-3.80	2	0.87	0.11-3.12	0.8573
	Grade 3	0	0.00	0.00-0.81	0	0.00	0.00-1.60	0	0.00	0.00-1.60	-
Non-solicited adverse reactions											
	Any	11	2.43	1.22-4.30	6	2.63	0.97-5.64	3	1.31	0.27-3.78	0.5624
	Grade 3	0	0.00	0.00-0.81	0	0.00	0.00-1.60	0	0.00	0.00-1.60	-

Abbreviations: N, number of participants in the total vaccinated cohort for safety. n, number of participants with the corresponding adverse reaction.%, incidence of the corresponding adverse reaction percent.