Vaccine 37 (2019) 1876–1884

Contents lists available at ScienceDirect

Vaccine

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

# Efficacy, immunogenicity, and safety of a quadrivalent inactivated influenza vaccine in children aged 6–35 months: A multi-season randomised placebo-controlled trial in the Northern and Southern Hemispheres

Stephanie Pepin [a,*], Martin Dupuy [a], Charissa Fay Corazon Borja-Tabora [b], May Montellano [c], Lulu Bravo [d], Jaime Santos [e], Jo-Anne de Castro [f], Doris Maribel Rivera-Medina [g], Clare Cutland [h], Miguel Ariza [i], Javier Diez-Domingo [j], Celia Diaz Gonzalez [k], Federico Martinón-Torres [l,m], Efimia Papadopoulou-Alataki [n], Maria Theodoriadou [o], Marie Pierre Kazek-Duret [a], Sanjay Gurunathan [p], Iris De Bruijn [a], for the GQM05 Study Group

[a] Sanofi Pasteur, Marcy-l'Étoile, France
[b] Research Institute for Tropical Medicine, Muntinlupa City, Philippines
[c] Mary Chiles General Hospital, Manila, Philippines
[d] University of the Philippines Manila – National Institutes of Health, Manila, Philippines
[e] Philippine Children's Medical Center, Quezon City, Philippines
[f] DLSUMC De La Salle Health Sciences Institute, Dasmariñas, Cavite, Philippines
[g] Inversiones en Investigación Médica S.A, Tegucigalpa, Honduras
[h] Chris Hani Baragwanath Hospital, Johannesburg, South Africa
[i] Caimed Dominicana A.S. Investigacion en Salud, Santo Domingo, Dominican Republic
[j] FISABIO-Public Health, Valencia, Spain
[k] Hospital Infantil La Paz, Madrid, Spain
[l] Translational Pediatrics and Infectious Diseases, Universitario de Santiago de Compostela, Santiago de Compostela, Spain
[m] Genetics, Vaccines and Infectious Diseases Research Group (GENVIP), Instituto de Investigación Sanitaria de Santiago, Universidad de Santiago, Spain
[n] School of Medicine, Aristotle University of Thessaloniki, Thessaloniki, Greece
[o] Children's Hospital Aghia Sofia, Athens, Greece
[p] Sanofi Pasteur, Swiftwater, PA, USA

ARTICLE INFO

*Article history:*
Received 9 July 2018
Received in revised form 9 October 2018
Accepted 26 November 2018
Available online 14 December 2018

*Keywords:*
Quadrivalent inactivated influenza vaccine
Children
Efficacy
Safety
Immunogenicity

ABSTRACT

*Background:* A quadrivalent split-virion inactivated influenza vaccine (VaxigripTetra™, Sanofi Pasteur; IIV4) containing two A strains (H1N1 and H3N2) and B strains from both lineages (Victoria and Yamagata) was approved in Europe in 2016 for individuals aged ≥ 3 years. This study examined the efficacy and safety of IIV4 in children aged 6–35 months.

*Methods:* This was a phase III randomised controlled trial conducted in Latin America, Asia, Africa, and Europe during the Northern Hemisphere 2014/2015 and 2015/2016 and Southern Hemisphere 2014 and 2015 influenza seasons. Healthy children aged 6–35 months not previously vaccinated against influenza were randomised to receive two full doses 28 days apart of IIV4, placebo, the licensed trivalent split-virion inactivated vaccine (IIV3), an investigational IIV3 containing a B strain from the alternate lineage. The primary objective was to demonstrate efficacy against influenza illness caused by any strain or vaccine-similar strains.

*Results:* The study enrolled 5806 participants. Efficacy, assessed in 4980 participants completing the study according to protocol, was demonstrated for IIV4. Vaccine efficacy was 50.98% (97% CI, 37.36–61.86%) against influenza caused by any A or B type and 68.40% (97% CI, 47.07–81.92%) against influenza caused by vaccine-like strains. Safety profiles were similar for IIV4, placebo, and the IIV3s, although

* Corresponding author at: Sanofi Pasteur, 1541 Avenue Marcel Mérieux, 69280 Marcy-l'Étoile, France.

*E-mail addresses:* Stephanie.Pepin@sanofipasteur.com, stephanie.pepin@sanofi.com (S. Pepin), Martin.Dupuy@sanofi.com (M. Dupuy), jimson2@me.com (J. Santos), cutlandc@rmpru.co.za (C. Cutland), celiac.diaz@salud.madrid.org (C.D. Gonzalez), Federico.Martinon.Torres@sergas.es (F. Martinón-Torres), efiala@otenet.gr (E. Papadopoulou-Alataki), mpapagrig@med.uoa.gr (M. Theodoriadou), Marie-Pierre.Kazek-Duret@sanofi.com (M.P. Kazek-Duret), Sanjay.Gurunathan@sanofi.com (S. Gurunathan), Iris.DeBruijn@sanofi.com (I. De Bruijn).

https://doi.org/10.1016/j.vaccine.2018.11.074

injection-site reactions were slightly more frequent for IIV4 than placebo.
*Conclusions:* IIV4 was safe and effective for protecting children aged 6–35 months against influenza illness caused by vaccine-similar or any circulating strains.
*Clinical trial registration:* EudraCT no. 2013-001231-51.


## 1. Introduction

Influenza is a highly contagious viral infection and a significant burden especially for children due to an increased risk for severe illness and hospitalisation [1,2]. Although influenza A has historically been considered more important, influenza B is now known to be a significant cause of influenza-related illness, hospitalisation, and death [3] and to cause epidemics every 2–4 years [3,4]. Influenza B is a particular concern in young children in whom it causes a disproportionate amount of severe illness and hospitalisation [3,5].

In the 1980s, influenza B viruses diverged into two immunologically distinct lineages, Victoria and Yamagata, which now co-circulate worldwide [6]. Because trivalent influenza vaccines contain only a single B-lineage strain and because circulation varies between seasons and regions, differences between the vaccine and dominant circulating B-lineages are common [7,8]. Due to limited cross-lineage protection [9,10], especially in young children [11], quadrivalent influenza vaccines containing both B lineages may reduce the risk of influenza illness and its associated morbidity and mortality [12].

A quadrivalent split-virion inactivated influenza vaccine (IIV4[1]; VaxigripTetra™, Sanofi Pasteur) has been available in Europe since 2016 for individuals aged ≥ 3 years. Phase III clinical trials in individuals ≥ 3 years demonstrated that IIV4 was as immunogenic as the comparator trivalent inactivated influenza vaccine (IIV3) for each of the three shared influenza strains and superior for the additional B strain [13–16]. These trials also showed that IIV4 has a similar safety and reactogenicity profile as the licensed IIV3 (Vaxigrip®, Sanofi Pasteur).

Because few studies had reported efficacy of inactivated influenza vaccines in very young children, in 2012, the World Health Organization (WHO) stated that they had only moderate confidence in their efficacy for this population [17]. To assess IIV4 in young children and to help reduce this evidence gap, we performed a phase III placebo-controlled clinical trial in which the primary objective was to demonstrate efficacy in children aged 6–35 months. Importantly, the vaccine used in this study contained a full dose of antigen (15 μg hemagglutinin [HA] per strain) rather than a half dose (7.5 μg HA per strain), which has been used in this age group for >30 years. A half dose of antigen was originally intended to reduce the risk of convulsions associated with earlier whole-virus influenza vaccines [18], but more recent findings suggest that a full dose can be used in children <3 years to improve immunogenicity without increasing fever or other reactions [19–21].

[1] Abbreviations: CI, confidence interval; GMT, geometric mean titre; HA, hemagglutinin; HAI, hemagglutination inhibition; IIV3-1, investigational trivalent split-virion inactivated vaccine containing the B lineage (Victoria) not recommended by the World Health Organization; IIV3, split-virion inactivated vaccine; IIV3-2, licensed trivalent split-virion inactivated vaccine containing the B lineage (Yamagata) recommended by the World Health Organization; IIV4, quadrivalent split-virion inactivated influenza vaccine; NA, neuraminidase; RT-PCR, reverse transcription-polymerase chain reaction; VE, vaccine efficacy; WHO, World Health Organization.

## 2. Materials and methods

### 2.1. Study design

This was a phase III, randomised, placebo-controlled trial conducted between March 2014 and July 2016 at 49 centres in Asia, Latin America, Europe, and Africa (EudraCT no. 2013-001231-51).[2] The study included healthy children aged 6–35 months who had not been previously vaccinated for or infected with influenza according to participants' parents or guardians. Children aged < 24 -months had to be born at full term (≥37 weeks) or with a birth weight ≥ 2.5 kg. Further exclusion criteria are listed in Table S1. The primary objective was to demonstrate the clinical efficacy of two full doses (15 μg HA/strain) of IIV4 to prevent laboratory-confirmed influenza illness caused by any influenza A or B types or caused by vaccine-similar strains. Key secondary objectives were to demonstrate non-inferiority of hemagglutination inhibition (HAI) geometric mean titres (GMTs) for strains shared by IIV4 and IIV3; demonstrate superiority of HAI GMTs for B-lineage strains not shared between IIV4 and IIV3; and describe the immunogenicity and safety of all vaccines. The study design, including the influenza seasons, countries, randomisation schemes, participants included in the analyses for the different outcomes, and data monitoring are summarised in Fig. 1.

During the efficacy evaluation period, participants were randomised to receive two 0.5-ml doses 28 days apart (window +7 days) of IIV4 containing the WHO-recommended A(H3N2), A (H1N1), B/Yamagata-lineage, and B/Victoria-lineage strains; an investigational IIV3 containing the WHO-recommended A strains and a strain from the B lineage not recommended by the WHO (Victoria) (IIV3-1); the licensed IIV3 containing the WHO-recommended A and B (Yamagata lineage) strains (IIV3-2); or placebo (saline). Efficacy was assessed only in participants vaccinated with IIV4 or placebo, whereas blood samples were taken for immunogenicity testing from all participants 28 days after the second vaccination.

A randomly selected subset of participants who had received IIV4 or placebo during the 2014/2015 season was asked to return during the 2015/2016 season to be vaccinated with IIV4 (revaccination period). Those who had received IIV4 during the 2014/2015 season were vaccinated with a single 0.5-ml dose of IIV4, whereas those who had received placebo were vaccinated with two 0.5-ml doses of IIV4 28 days apart (window ±14 days). Blood samples were taken for immunogenicity testing 28 days after each vaccination.

### 2.2. Randomisation and blinding

Randomisation lists were generated with the permuted block method and were communicated via an interactive voice or web-response system. The study was single (observer)-blinded for the IIV4 and placebo groups and, due to differences in study procedures, open label for IIV3-1 and IIV3-2.

[2] The protocol for this clinical trial is available at https://www.clinicaltrialsregister.eu/.

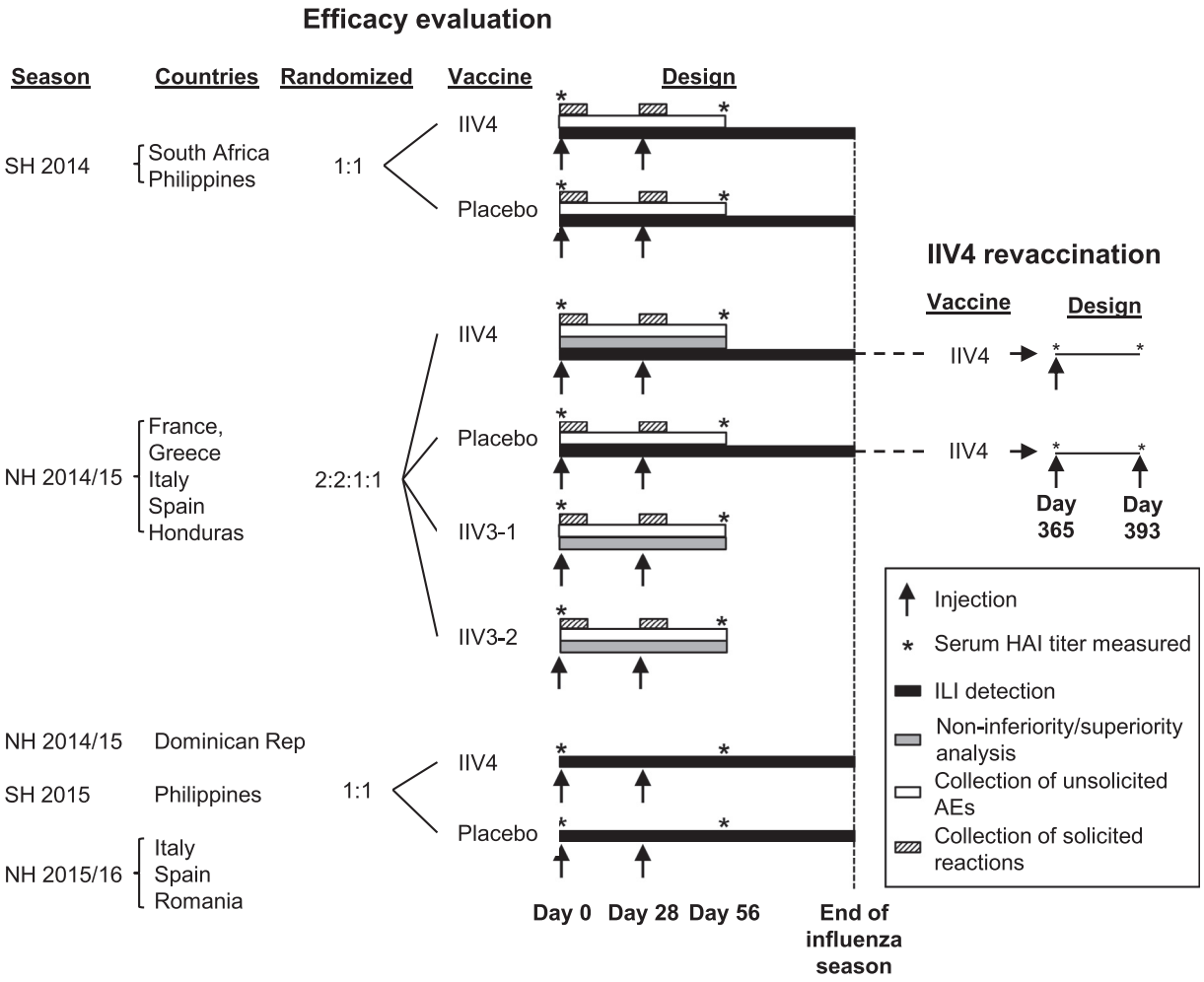


**Fig. 1.** Study design. The efficacy evaluation period was conducted in three cohorts: during the SH 2014 season in South Africa and The Philippines, participants were randomised 1:1 to IIV4 or placebo; during the NH 2014/2015 season in France, Greece, Italy, Spain, and Honduras, participants were randomised 2:2:1:1 to IIV4, placebo, IIV3-1, or IIV3-2; and during the NH 2014/2015 (Dominican Republic), SH 2015 (Philippines), and NH 2015/2016 (Italy, Spain, and Romania) seasons, participants were randomised 1:1 to IIV4 or placebo. During the revaccination period, a randomly selected subset of participants who had been vaccinated with IIV4 or placebo during the NH 2014/2015 season were invited to come back the following (2015/2016) season to be vaccinated with IIV4. Influenza cases and efficacy data were reviewed periodically by an independent data monitoring committee, and blinded safety data were reviewed by an internal safety management team. Abbreviations: AE, adverse event; HAI, hemagglutination inhibition; IIV3-1, trivalent influenza vaccine containing the B-lineage strain not recommended by the World Health Organization; IIV3-2, trivalent influenza vaccine containing the B-lineage strain recommended by the World Health Organization; IIV4, quadrivalent split-virion inactivated influenza vaccine; ILI, influenza-like illness; NH, Northern Hemisphere; Rep, Republic; SH, Southern Hemisphere.

### 2.3. Ethics

The study was approved by the independent ethics committee or institutional review board for each study site and was conducted in accordance with Good Clinical Practice and the Declaration of Helsinki. Written informed consent was provided by the parents or legal representatives of all children participating in this trial.

### 2.4. Vaccines

All vaccines were thimerosal-free, inactivated, split-virion, and contained 15 μg of HA from each strain per 0.5-ml dose. Vaccines and placebo were presented in 0.5-ml prefilled syringes and were administered by intramuscular or deep subcutaneous injection into the deltoid region or the thigh. Vaccine formulations and strains used in the study are summarised in Table S2.

### 2.5. Detection of influenza and analysis of similarity to vaccine strains

The occurrence of influenza-like illness was followed from 14 days after the second vaccine dose until the end of October for Asia and Africa and the end of April for Europe and Latin America. Participants were considered to have influenza-like illness if they had a fever ≥38 °C lasting ≥24 h concurrently with cough, nasal congestion, rhinorrhoea, pharyngitis, otitis, vomiting, or diarrhoea. For participants diagnosed with influenza-like illness, a nasopharyngeal swab was taken for laboratory confirmation of influenza within 10 days after onset.

Nasopharyngeal swab samples from subjects with influenza-like illness were used to inoculate and infect influenza virus-susceptible tissue culture cell lines. Influenza positive cultures were confirmed by direct immunofluorescence techniques with influenza type-specific (i.e., for influenza A and influenza B) antibodies. For culture confirmation of influenza, three different culture cell lines were utilised for each nasopharyngeal sample: classic influenza A and B culture using Madin-Darby canine kidney cells; classic influenza A and B culture using rhesus monkey kidney cells; and R Mix (a mixed monolayer of human A549 lung carcinoma and mink lung cells).

Clinical samples collected during the study period underwent an extraction procedure to isolate the viral RNA from nasopharyngeal swabs prior to testing. The initial molecular test was a reverse

transcription-polymerase chain reaction (RT-PCR)-based assay (eSensor Respiratory Viral Panel, GenMark) to determine if influenza A, influenza A H1 seasonal subtype, influenza A H3 seasonal subtype, influenza A 2009 H1N1 subtype, or influenza B were present in the clinical sample.

For samples that were positive for influenza based on viral culture or RT-PCR, further testing by Sanger sequencing of the HA and neuraminidase (NA) full-gene segments was performed to identify the specific type or sub-type of the influenza strain. For genetic sequencing of HA and NA gene segments, total nucleic acid was extracted from the specimen/samples on an automated extraction system. Regions of both HA and NA genes were amplified by RT-PCR using H1N1, H3N2 and B strain-specific primers. Amplified products were purified by plate filtration, and cycle sequencing reactions were performed on purified amplicons using fluorescently labelled dideoxy terminators. Cycle sequencing reaction products were purified by precipitation and analysed by agarose gel electrophoresis on an automated genetic analyser.

The raw genetic sequence of each positive sample was compared with a database of known sequences corresponding to the vaccine and major circulating strains from 2005 up to the time of testing. Upon completion of sequencing runs, consensus sequences were compared to the Sanofi Pasteur reference BLAST database to determine closely related sequences. The best match had to be ≥95% alignment length and ≥99% identity. If a sequence did not meet these criteria, it was used as a query against the current version of National Center for Biotechnology Information Influenza Virus Resource Database.

The strain responsible for laboratory-confirmed influenza was based on the Sanger sequencing results of the full HA gene, although if the RT-PCR results indicated A/H1N1 2009 pandemic influenza, the strain was considered to be A/California/7/2009. The strain responsible for a laboratory-confirmed influenza case was considered as similar to a strain contained in the vaccine if the best match strain was the same as any of the vaccine strains.

### 2.6. HAI titres

Serum HAI titres were measured as described previously [22] for a randomly selected subset of participants included in the efficacy evaluation period (see Fig. 1) and for all participants included in the revaccination period. Seroconversion was defined as a HAI titre <10 on day 0 and a HAI titre ≥40 measured 28 days after the last vaccination. A significant increase was defined as a HAI titre ≥10 on day 0 and a ≥4-fold increase from baseline in HAI titre 28 days after the last vaccination.

### 2.7. Solicited reactions and adverse events

Solicited reactions were collected by parents and legal guardians, and unsolicited adverse events were recorded by investigators (see Fig. 1 for subsets included). Solicited injection-site reactions included tenderness for participants aged 6–23 months; pain for participants 24–35 months; and erythema, swelling, induration, and ecchymosis for all participants. Solicited systemic reactions included vomiting, abnormal crying, drowsiness, loss of appetite, and irritability for participants aged 6–23 months; headache, malaise, myalgia, and shivering for participants aged 24–35 months; and fever for all participants. Investigators also recorded serious adverse events and adverse events of special interest up to 6 months after each injection. Adverse events and serious adverse events were recorded according to International Conference for Harmonization guidelines [23].

### 2.8. Statistical analysis

The co-primary outcomes were vaccine efficacy (VE) in preventing laboratory-confirmed influenza caused by (i) any A or B strain and (ii) vaccine-similar strains. Both were assessed in all randomised participants in the IIV4 and placebo groups without relevant protocol violations and according to the vaccine to which they were randomised. Sensitivity analysis was performed in the full set of randomised patients who received two doses of vaccine. VE was calculated as 100% × (1 − [number of confirmed influenza cases in the IIV4 group/total number of participants in the IIV4 group]/[number of influenza cases in the placebo group/total number of participants in the placebo group]). Confidence intervals (CIs) for VE were calculated by an exact method assuming a binomial distribution of the number of cases in each vaccine group conditional on the total number of cases. The co-primary endpoints were assessed using a one-sided 0.015 nominal alpha, resulting in a two-sided 97% CI. For each of the co-primary outcomes, efficacy was considered demonstrated if the lower-bound of the 97% CI for the corresponding VE was >20%. The primary objective was considered to have been met if efficacy was demonstrated for either of the co-primary outcomes.

Approximately 553 evaluable influenza cases were needed to provide approximately 80% power to draw a conclusion of VE (primary objective) assuming that the true VE for IIV4 is 45% against vaccine-similar influenza strains and 0% against other strains; an adjusted one-sided type I error rate of 0.01247; a lower-bound of the CI of VE >20% for at least one primary outcome; and an allocation ratio of IIV4 to placebo of 1:1. Considering an overall influenza attack rate of 9% for the occurrence of an influenza case in the placebo group and 90% of enrolled participants evaluable for the primary outcome, a total of 8536 participants were estimated to be needed to be enrolled for influenza surveillance to reach the 553 expected evaluable influenza cases.

Non-inferiority of HAI titres was assessed according to the vaccine received in randomised participants who completed the vaccination schedule, had a blood sample drawn 28–35 days after the last dose, and completed the efficacy evaluation period according to protocol. For each strain, non-inferiority was demonstrated if the two-sided 95% CI of the ratio of the geometric mean HAI titre (GMT) between IIV4 and IIV3 containing the same B-lineage strain, calculated using a normal approximation of log-transformed titres, was >2/3. Superiority was assessed in randomised participants who received at least one dose of vaccine and had a blood sample drawn 28–35 days after the last dose. For each B strain, superiority was demonstrated if the two-sided 95% CI of the ratio of the GMT between IIV4 and IIV3 containing the alternate B-lineage strain, calculated using a normal approximation of log-transformed titres, was >1.

There were to be approximately 464 subjects assessed for HAI immunogenicity in the IIV4 group and 232 subjects in each IIV3 group. This was to produce an overall power of 90% to demonstrate: (a) non-inferiority of IIV4 vs. IIV3 in terms of HAI GMTs with a one-sided alpha level of 2.5%, a non-inferiority margin of 1.5, a theoretical ratio of 1:1 between groups, assuming a standard deviation of $\log_{10}$-transformed titres of 0.6 for A strains and 0.5 for B strains, and 80% subjects evaluable; and (b) superiority of IIV4 vs. each IIV3 group for the B-lineage strain it did not contain assuming that the IIV4 induced at least a 2-fold increase in the IIV3 response to the B strain it did not contain, a standard deviation of $\log_{10}$-transformed titres of 0.5, and 90% subjects evaluable.

Statistical analysis was performed by Sanofi Pasteur (Marcy L'Etoile, France) using SAS® version 9.4 (SAS Institute, Cary, NC, USA). Missing data were not replaced.

### 2.9. Data monitoring, interim analysis, and stopping guidelines

Two interim analyses by an independent data monitoring committee were planned to determine if efficacy had been demonstrated. The first was conducted when 200 confirmed influenza cases had been detected. The second, planned for when 375 confirmed influenza cases had been detected, was not conducted because efficacy was demonstrated at the first interim analysis. Enrolment was to be stopped at either interim analysis if the primary objective of efficacy was met, if the predictive power to demonstrate the primary objective at the end of the ongoing season was high, or if the probability to demonstrate the primary objective at the end of the trial was too low.

## 3. Results

### 3.1. Participants

The study enrolled 5806 participants aged 6 to 35 months of which 5805 were randomised to receive two injections 28 days apart of IIV4 (n = 2721), placebo (n = 2715), IIV3-1 (n = 183), or IIV3-2 (n = 186) (Fig. 2). The study was conducted over four influenza seasons (Southern Hemisphere 2014 and 2015 and Northern Hemisphere 2014/2015 and 2015/2016) so that enrolment spanned 18 months from March 12, 2014 to December 4, 2015. Enrolment was stopped before the planned study size (8536 participants) was reached because efficacy was demonstrated during a planned interim analysis. A random subset of participants who had received IIV4 (n = 213) or placebo (n = 41) during the efficacy evaluation period were vaccinated with IIV4 the following season.

Sex, age, and prevalence of at-risk conditions were similar in the four study groups (Table 1). Regions and ethnicities were similar for the IIV4 and placebo groups but different from the IIV3 groups as a result of the study design (see Fig. 1). No participants left the study due to a vaccine-related adverse event.

### 3.2. Efficacy vs. laboratory-confirmed influenza illness

Of the 5436 participants in the IIV4 and placebo groups who completed the efficacy evaluation period, 456 were not included in the per-protocol efficacy analysis because of protocol violations or deviations. Thus, efficacy was assessed in 4980 participants. Laboratory-confirmed influenza illness was detected in 365 participants, including 120 (4.8%) in the IIV4 group and 245 (9.8%) in the placebo group. Influenza was due to vaccine-similar strains for 100 of the 365 participants with laboratory-confirmed illness (24 for IIV4 and 76 for placebo). By strain, confirmed influenza cases were most commonly due to influenza B (n = 164) and A/H3N2 (n = 156). Influenza A/H1N1 was relatively uncommon (n = 55). The strains detected and their similarity to the vaccine strains are listed in Table S3.

The primary objective of efficacy was demonstrated for IIV4, with a VE vs. influenza due to any A or B type of 50.98% (97% CI, 37.36–61.86%) and vs. influenza due to a vaccine-like strain of 68.40% (97% CI, 47.07–81.92%) (Table 2). Results were similar when assessed in the full set of participants vaccinated with two doses of vaccine (Table S4). VE values for IIV4 were also similar when calculated separately for RT-PCR-confirmed influenza and culture-confirmed influenza and when analysed separately for influenza A, A(H1N1), A(H3N2), B, and B/Yamagata, although not for B/Victoria (Table 2). For the four influenza seasons included, VE ranged

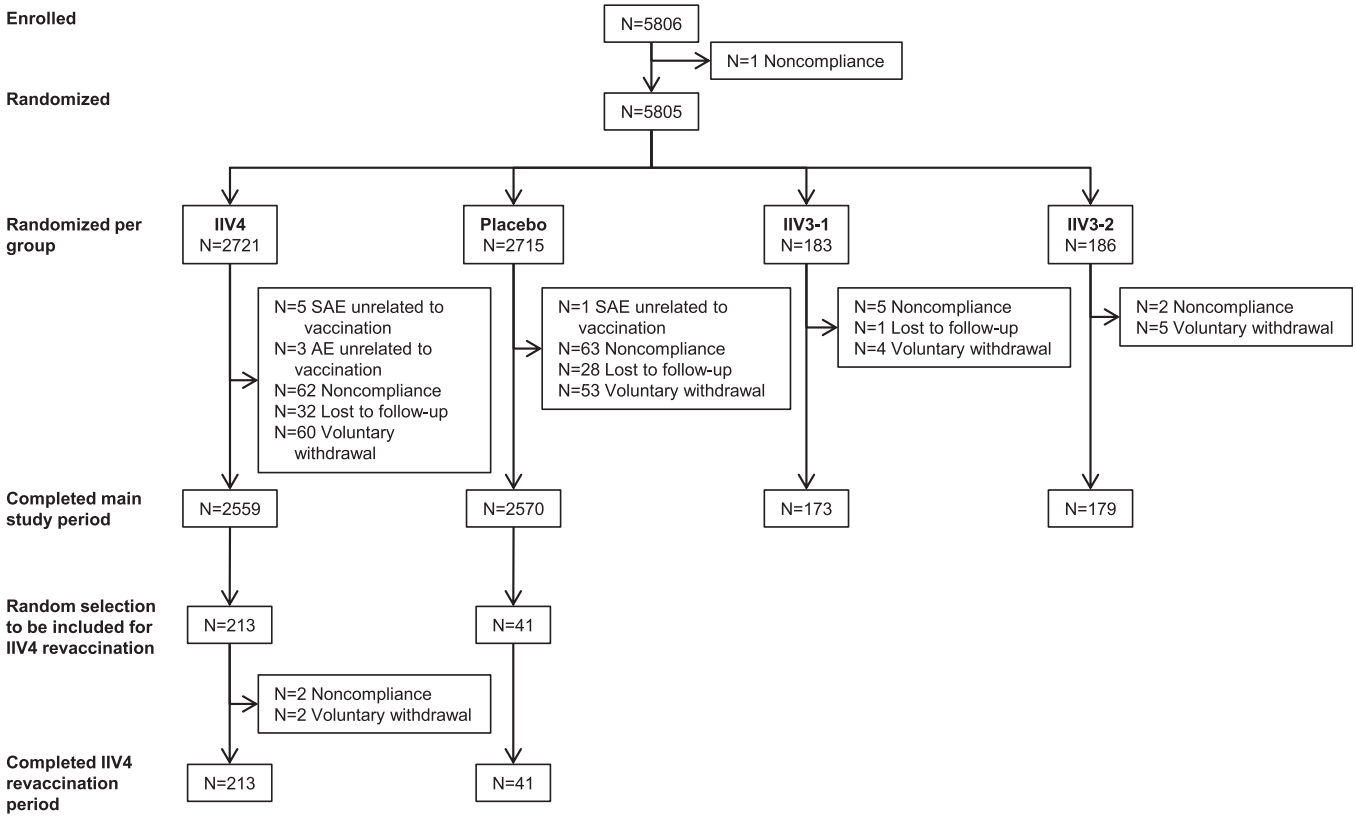


**Fig. 2.** Participant disposition. Abbreviations: AE, adverse event; IIV3-1, trivalent influenza vaccine containing the B-lineage strain not recommended by the World Health Organization; IIV3-2, trivalent influenza vaccine containing the B-lineage strain recommended by the World Health Organization; IIV4, quadrivalent split-virion inactivated influenza vaccine; SAE, serious adverse event.

**Table 1**
Participant demographics and baseline characteristics.

| Characteristic | IIV4 N = 2721 | Placebo N = 2715 | IIV3-1 N = 183 | IIV3-2 N = 186 |
|---|---|---|---|---|
| Sex, n (%) | | | | |
| Male | 1388 (51.0) | 1425 (52.5) | 94 (51.4) | 98 (52.7) |
| Female | 1333 (49.0) | 1209 (47.5) | 89 (48.6) | 88 (47.3) |
| Age in months, mean ± SD | 19.7 ± 8.4 | 19.8 ± 8.4 | 19.7 ± 8.4 | 19.3 ± 8.1 |
| At risk for influenza-related complications[a], n (%) | 30 (1.1) | 30 (1.1) | 3 (1.6) | 3 (1.6) |
| Ethnicity, n (%) | | | | |
| White | 505 (18.6) | 507 (18.7) | 76 (41.5) | 76 (40.9) |
| Asian | 1504 (55.3) | 1504 (55.4) | 0 (0.0) | 3 (1.6) |
| Black or African American | 261 (9.6) | 252 (9.3) | 3 (1.6) | 2 (1.1) |
| American Indian [b] or Alaska Native | 207 (7.6) | 205 (7.6) | 102 (55.7) | 102 (54.8) |
| Native Hawaiian or Pacific Islander | 0 (0.0) | 1 (<0.1) | 0 (0.0) | 0 (0.0) |
| Region, n (%) | | | | |
| Africa | 251 (9.2) | 249 (9.2) | – | – |
| Asia | 1498 (55.1) | 1501 (55.3) | – | – |
| Europe | 528 (19.4) | 523 (19.3) | 81 (44.3) | 84 (45.2) |
| Latin America | 444 (16.3) | 442 (16.3) | 102 (55.7) | 102 (54.8) |

Values are for all randomised participants. Abbreviations: IIV3-1, investigational trivalent split-virion inactivated vaccine containing the B lineage (Victoria) not recommended by the World Health Organization; IIV3-2, licensed trivalent split-virion inactivated vaccine containing the B lineage (Yamagata) recommended by the World Health Organization; IIV4, quadrivalent split-virion inactivated influenza vaccine; SD, standard deviation.
[a] Participants were considered to be at risk for influenza-related complications if they had chronic respiratory, heart, renal, metabolic, or haematological disorders.
[b] Latin American participants were classified as American Indian.

**Table 2**
Efficacy of the quadrivalent influenza vaccine by laboratory confirmation method and strain.

| Outcome | IIV4 n (%) N = 2489 | Placebo n (%) N = 2491 | Vaccine efficacy |
|---|---|---|---|
| *Primary outcome* | | | *% (97% CI)* |
| Laboratory-confirmed influenza illness caused by | | | |
| Any influenza A or B type | 120 (4.82) | 245 (9.84) | 50.98 (37.36; 61.86) |
| Vaccine-similar strains | 24 (0.96) | 76 (3.05) | 68.40 (47.07; 81.92) |
| *Secondary outcomes* | | | *% (95% CI)* |
| RT-PCR-confirmed influenza illness caused by | | | |
| Any influenza A or B type | 118 (4.74) | 243 (9.76) | 51.40 (39.20, 61.33) |
| Vaccine-similar strains | 24 (0.96) | 76 (3.05) | 68.40 (49.42, 80.91) |
| Culture-confirmed influenza illness | | | |
| Caused by any influenza A or B type | 91 (3.66) | 214 (8.59) | 57.44 (45.36, 67.07) |
| Caused by vaccine-similar strains | 22 (0.88) | 74 (2.97) | 70.25 (51.56, 82.40) |
| Laboratory-confirmed influenza illness by strain | | | |
| Any influenza A | 65 (2.61) | 147 (5.90) | 55.75 (40.35, 67.47) |
| A(H1N1) | 11 (0.44) | 44 (1.77) | 74.98 (50.77, 88.35) |
| A(H3N2) | 53 (2.13) | 103 (4.13) | 48.50 (27.59, 63.75) |
| Any influenza B | 58 (2.33) | 106 (4.26) | 45.24 (23.88, 60.94) |
| B/Victoria lineage | 12 (0.48) | 20 (0.80) | 39.95 (−28.98, 73.24) |
| B/Yamagata lineage | 26 (1.04) | 63 (2.53) | 58.70 (33.81, 74.90) |

Values are for participants with efficacy data completing the efficacy evaluation period according to protocol. Abbreviations: CI, confidence interval; IIV4, quadrivalent split-virion inactivated influenza vaccine; RT-PCR, reverse transcription-polymerase chain reaction.

from 41.2% to 59.6%, and for the two IIV4 formulations used, VE was 45.8% and 57.9% (Table S5).

### 3.3. Immunogenicity

At baseline, most participants were seronegative for each vaccine strain in IIV4 (Tables S6 and S7), with the exception of participants in Asia during the Southern Hemisphere 2014 season of whom 49.6% were seronegative. After vaccination with two doses of IIV4 (day 56), for each strain, <2% of participants remained seronegative. Post-vaccination HAI GMTs ranged from 445 to 819 for A(H1N1), 517 to 1901 for A(H3N2), 416 to 1183 for B/Victoria, and 783 to 1610 for B/Yamagata. Geometric mean post-/pre-vaccination ratios of HAI titres ranged from 34.9 to 61.3 for A (H1N1), 32.7 to 63.4 for A(H3N2), 70.4 to 122 for B/Victoria, and 68.2 to 275 for B/Yamagata. Rates of seroconversion or significant increase in titre were ≥87% for all strains.

Irrespective of the serological status at baseline, HAI antibody titres increased markedly after two injections of IIV4, although HAI GMTs were higher in participants with detectable titres (≥10) at baseline than in participants with undetectable titres (<10) (2149 vs. 408 for A(H1N1), 3632 vs. 585 for A(H3N2), 3986 vs. 562 for B/Victoria, and 1698 vs. 870 for B/Yamagata) (Table S8).

Non-inferiority of post-vaccination HAI titres for IIV4 was demonstrated for both A strains when compared to the pooled IIV3s (Table 3). Non-inferiority was also demonstrated for B/Yamagata when compared to the IIV3 containing the same B strain (IIV3-2), although not for B/Victoria when compared to the IIV3 containing the same B strain (IIV3-1). However, for both B strains, superiority was demonstrated for IIV4 when compared to IIV3 con-

**Table 3**
Non-inferiority and superiority of antibody responses induced by the quadrivalent influenza vaccine vs. trivalent comparators.

| Analysis/strain | IIV4 | | IIV3 | | Ratio of GMTs (IIV4/IIV3) | Non-inferior/ superior |
|---|---|---|---|---|---|---|
| | N | Day 56 HAI GMT (95% CI) | N | Day 56 HAI GMT (95% CI) | | |
| Non-inferiority[a] | | | | | | |
| A(H1N1) | 300 | 650 (549, 769) | 320[c] | 629 (530, 746) | 1.03 (0.81, 1.31) | Yes |
| A(H3N2) | 300 | 1075 (917, 1261) | 320[c] | 989 (845, 1158) | 1.09 (0.87, 1.36) | Yes |
| B/Victoria lineage | 300 | 593 (519, 678) | 152[d] | 806 (657, 988) | 0.74 (0.58, 0.93) | No |
| B/Yamagata lineage | 300 | 997 (863, 1153) | 168[e] | 983 (824, 1172) | 1.01 (0.80, 1.28) | Yes |
| Superiority[b] | | | | | | |
| B/Victoria lineage | 341 | 623 (550, 706) | 179[e] | 10.0 (8.26, 12.1) | 62.33 (50.04, 77.64) | Yes |
| B/Yamagata lineage | 341 | 1010 (885, 1153) | 171[d] | 39.9 (31.2, 51.0) | 25.3 (19.63, 32.62) | Yes |

Non-inferiority was demonstrated if the two-sided 95% CI of the ratio of the HAI GMT between IIV4 and that of the comparator IIV3, calculated using a normal approximation of log-transformed titres, was >2/3. Superiority was demonstrated if the two-sided 95% CI of the ratio of the HAI GMT between IIV4 and that of the comparator IIV3, calculated using a normal approximation of log-transformed titres, was >1. Abbreviations: CI, confidence interval, GMT, geometric mean titre; HAI, hemagglutination inhibition, IIV3, trivalent inactivated split-virion influenza vaccine; IIV4, quadrivalent inactivated split-virion influenza vaccine.

[a] The primary analysis for non-inferiority was performed in all randomised participants who completed the vaccination schedule, had blood sample drawn after the last dose, and completed the efficacy evaluation period according to protocol.

[b] The primary analysis of superiority was performed in all randomised participants who received at least one dose of vaccine and had a blood sample drawn after the last dose.

[c] Comparator was pooled IIV3s (IIV3-1 and IIV3-2).

[d] Comparator was IIV3-1 (investigational IIV3 containing the B/Victoria lineage).

[e] Comparator was IIV3-2 (licensed IIV3 containing the B/Yamagata lineage).

taining the alternate lineage (Table 3). Results were similar when the non-inferiority and superiority analyses were repeated in alternate data sets (Table S9).

During the revaccination period, HAI GMTs at baseline (day 365) were higher in participants who had been vaccinated with IIV4 than in those who had been vaccinated with placebo (Fig. S1). After one dose of vaccine (day 393), HAI GMTs for each strain were at least four-fold higher in participants who had previously received IIV4 than in those who had previously received placebo.

### 3.4. Safety and reactogenicity

Except for a higher proportion of participants reporting solicited injection-site reactions in the IIV4 group (39.9% [95% CI, 37.5–42.4%]) than in the placebo group (31.9% [95% CI, 29.6–34.2%]), proportions reporting solicited reactions and adverse events were similar for the IIV4, IIV3, and placebo groups (Tables 4, S10, and S11). A single vaccine-related serious adverse event (benign febrile seizure) was reported for a participant vaccinated with IIV4. The event was secondary to an upper respiratory tract infection, did not lead to study discontinuation, and the participant recovered.

## 4. Discussion

This randomised, placebo-controlled study confirmed the clinical efficacy of two full doses of IIV4 (15 μg HA/strain) for preventing influenza in children aged 6–35 months. Efficacy was demonstrated against vaccine-similar strains as well as against any strain, even though only about one-quarter of confirmed infections were due to vaccine-similar strains. The level of efficacy observed here is similar to that reported for another full-dose inactivated quadrivalent influenza vaccine in this same age group [24]. Together, the results provide convincing evidence that inactivated quadrivalent influenza vaccines are effective at preventing influenza in children aged 6–35 months.

This study also showed that a full dose of IIV4 could be safely administered to young children. With the exception of more frequent injection-site reactions with IIV4 than with placebo, the overall safety profile for IIV4 appeared similar to placebo and IIV3. This agrees with other studies showing that a full dose of antigen can be used to increase the immune response to influenza vaccines in young children without adversely affecting safety [19–21,24,25]. Furthermore, adding a fourth strain and using a full dose of antigen (15 μg HA/strain) appeared acceptable for this age group.

**Table 4**
Adverse events and solicited reactions.

| Event | IIV4 | | Placebo | | Pooled IIV3 | |
|---|---|---|---|---|---|---|
| | n/N | % (95% CI) | n/N | % (95% CI) | n/N | % (95% CI) |
| Immediate unsolicited adverse event (<30 min) | 1/1614 | <0.1 (0.0, 0.3) | 2/1612 | 0.1 (0.0, 0.4) | 1/367 | 0.3 (0.0, 1.5) |
| Vaccine-related | 1/1614 | <0.1 (0.0, 0.3) | 1/1612 | <0.1 (0.0, 0.3) | 0/367 | 0.0 (0.0, 1.0) |
| Solicited reaction ≤ 7 days after vaccination | 1017/1592 | 63.9 (61.5, 66.2) | 921/1595 | 57.7 (55.3, 60.2) | 216/362 | 59.7 (54.4, 64.8) |
| Injection-site | 635/1591 | 39.9 (37.5, 42.4) | 508/1593 | 31.9 (29.6, 34.2) | 124/361 | 34.3 (29.5, 39.5) |
| Systemic | 772/1592 | 48.5 (46.0, 51.0) | 741/1595 | 46.5 (44.0, 48.9) | 180/362 | 49.7 (44.5, 55.0) |
| Unsolicited adverse event ≤ 28 days after vaccination | 1044/1614 | 64.7 (62.3, 67.0) | 1079/1612 | 66.9 (64.6, 69.2) | 261/367 | 71.1 (66.2, 75.7) |
| Vaccine-related | 91/1614 | 5.6 (4.6, 6.9) | 96/1612 | 6.0 (4.9, 7.2) | 7/367 | 1.9 (0.8, 3.9) |
| Leading to study discontinuation | 3/1614 | 0.2 (0.0, 0.5) | 0/1612 | 0.0 (0.0, 0.2) | 0/367 | 0.0 (0.0, 1.0) |
| Serious adverse event ≤ 180 days after vaccination | 68/1614 | 4.2 (3.3, 5.3) | 78/1612 | 4.8 (3.8, 6.0) | 14/367 | 3.8 (2.1, 6.3) |
| Death[a] | 4/1614 | 0.2 (0.1, 0.6) | 1/1612 | <0.1 (0.0, 0.3) | 0/367 | 0.0 (0.0, 1.0) |
| Adverse event of special interest[b] | 29/2718 | 1.1 (0.7, 1.5) | 31/2711 | 1.1 (0.8, 1.6) | 1/367 | 0.3 (0.0, 1.5) |

Values are for all participants who received at least one dose of vaccine or placebo. Abbreviations: CI, confidence interval, IIV3, trivalent inactivated split-virion influenza vaccine, IIV4, quadrivalent inactivated split-virion influenza vaccine.

[a] None of the deaths were considered vaccine-related.

[b] Included anaphylaxis, Guillain-Barre syndrome, encephalitis/myelitis, neuritis, febrile convulsions, non-febrile convulsions, thrombocytopenia, and vasculitis.

Immunogenicity is used as a correlate of protection, but identifying a clear threshold for protection has been difficult, especially for young children [26,27]. Because of this and to help strengthen the evidence base supporting efficacy of inactivated influenza vaccines in very young children, the study focused on demonstrating efficacy, with immunogenicity as a secondary and supporting endpoint. The study demonstrated that IIV4 induced high HAI antibody titres in this population and that it provided superior titres for the added B-lineage strain and non-inferior titres vs. IIV3 for all shared strains, except for B/Victoria. This lack of non-inferiority for the B/Victoria strain does not appear to be a general feature of IIV4 because non-inferiority against all vaccine strains has been demonstrated for individuals aged ≥3 years [22,28]. Whether this unexpected finding will prove to be common for very young children will require further study.

This study was designed to include unprimed young children. According to parents and guardians, the participants had not been previously vaccinated for influenza or infected with influenza virus. Nevertheless, depending on the region and season, up to half of the participants had detectable baseline HAI titres for each strain, suggesting that they had, in fact, been exposed to influenza viruses. As expected, post-vaccination titres were higher in these participants, although the IIV4 was highly immunogenic even in participants without detectable baseline antibodies.

The revaccination portion of the study revealed that the antibody titres induced by a single dose of IIV4 increased when the participants had received IIV4 the previous season. This indicates that IIV4 could adequately prime this population. It also suggests that the two-dose schedule currently recommended for vaccinating unprimed children aged <9 years [29] should be continued for the full dose of IIV4.

A major strength of this study was its representativeness. It was a large study conducted over a wide geographical area in both hemispheres and over several influenza seasons. The study was, however, limited by the vaccine strains that circulated. During the four seasons included, influenza A(H3N2) and B/Yamagata strains dominated. Thus, efficacy could be demonstrated against the A/H1N1, A/H3N2, and B/Yamagata strains but not against the B/Victoria strain. Efficacy of IIV4 against the B/Victoria strain will have to be established in further studies.

In conclusion, this study showed that IIV4 safely protected children aged 6–35 months against influenza illness. By including a second B-lineage strain, IIV4 should provide additional protection beyond IIV3, irrespective of which B lineage circulates during a given season or region. As IIV4 gradually replaces IIV3 globally, it may help further reduce influenza-associated morbidity and mortality in young children.

## Acknowledgments

The study was funded by Sanofi Pasteur. Medical writing was provided by Dr. Phillip Leventhal (4Clinics, Paris, France) and paid for by Sanofi Pasteur. Employees of Sanofi Pasteur participated in conceiving and designing the study, drafting and editing the article, deciding to submit the article for publication, and approving the final, submitted version.

S.P. conceived and designed the study and helped draft the article; J.D.D., C.D.G., and F.M.T. participated in data acquisition. S.P., M.D., I.D.B., S.G., M.P.K., C.F.C., M.M., L.B., J.D.C., D.M.R.M., C.C., and M.A. participated in data analysis and interpretation. All authors helped critically revise the manuscript, approved the final version, and agree to be accountable for the accuracy and integrity of its content.

The members of the GQM05 study group included: Karina Abalos (Sanofi Pasteur, Taguig City, Philippines), Helena Aurell (Sanofi Pasteur, Marcy-l'Étoile, France), José Maria Baldó (Centro de Salud Quart de Poblet, Valencia, Spain), Gianni Bona (Universita del Piemonte Orientale, Novara, Italy), Miguel Angel Cabanero (Centro de Salud Illes Columbretes), Josefina Cadorna-Carlos (University of the East Ramon Magsaysay), Marcela Cangrejo (Sanofi Pasteur, Bogota, Columbia), Brindusa Ruxandra Capilna (Ultratest S.R.L., Târgu Mureș, Romania), Alexandra Carmen Cara (private practice, Călăraşi, Romania), Alfonso Carmona Martinez (Instituto Hispalense de Pediatria de Sevilla, Sevilla, Spain), Frédéric Chemin (private practice, Ecully, France), Ricardo Closa (Universitat Rovira i Virgili, Tarragona, Spain), Manuel Baca Cots (Hospital quirón salud), Florence Coux (Sanofi Pasteur, Marcy-l'Étoile, France), Javier Diez-Domingo (Centro Superior de Investigación en Salud Pública), Laura Larisa Dracea (private practice, Brasov, Romania), Maria Emporiadou (Aristotle University of Thessaloniki), María Espiau (University Hospital Vall d'Hebron, Barcelona, Spain), Susanna Esposito (Universita degli Studi, Genoa, Italy), Oana Asso Falup Pecurariu (Transylvania University, Brasov, Romania), Maria Garcés-Sanchez (Centro Superior de Investigación en Salud Pública, Valencia, Spain), Sanjay Garg (Sanofi Pasteur, Marcy-l'Étoile, France), Amparo Gil (Centro de Salud Malvarrosa), Laurie Gonzales (Sanofi Pasteur, Marcy-l'Étoile, France), Ronan Guevel (Sanofi Pasteur, Marcy-l'Étoile, France), Sara Guillen (Hospital Universitario de Getafe, Madrid, Spain), Giancarlo Icardi (Universita degli Studi, Genoa, Italy), Thelma Laot (Sanofi Pasteur, Manilla, Philippines), Isabelle Lacroix (Sanofi Pasteur, Marcy-l'Étoile, France), Josep Marès (Institut Pediàtric Marès-Riera, Girona, Spain), Manuel Martinez Pons (CS Republica Argentina), Catherine Moreau (Sanofi Pasteur, Marcy-l'Étoile, France), Mihai Leonida Neamtu (Lucian Blaga University of Sibiu, Sibiu, Romania), Andrea Elena Neculau (private practice, Brasov, Romania), Joyce Ojeda (Sanofi Pasteur, Mexico City, Mexico), Vana Papaevangelou (University of Athens School of Medicine, Athens, Greece), Maria Gabriella Penon (ULSS179 Presidio Ospedaliero di Este Dipartimento (PD)), Celine Petit (Sanofi Pasteur, Marcy-l'Étoile, France), Marie Philibert (Sanofi Pasteur, Marcy-l'Étoile, France), Victoria Planelles Cantarino (Centro Superior de Investigación en Salud Pública, Valencia, Spain), Marie-Laure Py (Sanofi Pasteur, Marcy-l'Étoile, France), José T. Ramos (Hospital Clínico San Carlos), Enrique Rivas (Sanofi Pasteur, Mexico City, Mexico), Emmanouel Roilides (Aristotle University, Thessaloniki, Greece), Angels Rosich (Centro de Salud Malvarrosa, Valencia, Spain), Camille Salamand (Sanofi Pasteur, Marcy-l'Étoile, France), Eva Suarez (Centro de Salud Burriana 2), Gabriel Doru Surdu (private practice, Ploiești, Romania), Teresa Cerdán Vera (private practice, Valencia, Spain), Mariza Tsolia (University of Athens School of Medicine, Athens, Greece), Mira Vicedo (Centro de Salud Petrer 1), and Anne Woods (Sanofi Pasteur, Marcy-l'Étoile, France).

## Conflict of interest

C.C. reports grants from Sanofi Pasteur during the conduct of the study. J.D.D. reports other support from Sanofi Pasteur during the conduct of the study and personal fees from Sanofi Pasteur outside the submitted work. M.E.M. reports personal fees from Sanofi Pasteur and GlaxoSmithKline outside the submitted work. F.M.T. reports other support from Ablynx, Janssen, GlaxoSmithKline, Regeneron, Medimmune, Pfizer, MSD, and Sanofi Pasteur outside the submitted work; and personal fees from Pfizer, MSD, and Sanofi Pasteur outside the submitted work. D.M.R.M. reports grants from Sanofi Pasteur during the conduct of the study and outside the submitted work. S.P, M.D., M.P.K.D., S.G., and I.D.B. are employees of Sanofi Pasteur. All others declare no conflicts of interest.

## Author contributions

All authors attest they meet the ICMJE criteria for authorship.

## Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.vaccine.2018.11.074.

## References


[1] Fraaij PL, Heikkinen T. Seasonal influenza: the burden of disease in children. Vaccine 2011;29:7524–8.
[2] Iskander M, Booy R, Lambert S. The burden of influenza in children. Curr Opin Infect Dis 2007;20:259–63.
[3] Glezen PW, Schmier JK, Kuehn CM, Ryan KJ, Oxford J. The burden of influenza B: a structured literature review. Am J Public Health 2013;103:e43–51.
[4] Thompson WW, Shay DK, Weintraub E, Brammer L, Cox N, Anderson LJ, et al. Mortality associated with influenza and respiratory syncytial virus in the United States. JAMA 2003;289:179–86.
[5] World Health Organization. Review of the 2010–2011 winter influenza season, northern hemisphere. Rel Epidemiol Hebdomad 2011;86:222–7.
[6] Rota PA, Wallis TR, Harmon MW, Rota JS, Kendal AP, Nerome K. Cocirculation of two distinct evolutionary lineages of influenza type B virus since 1983. Virology 1990;175:59–68.
[7] Heikkinen T, Ikonen N, Ziegler T. Impact of influenza B lineage-level mismatch between trivalent seasonal influenza vaccines and circulating viruses, 1999–2012. Clin Infect Dis: Off Publ Infect Dis Soc Am 2014;59:1519–24.
[8] Crepey P, de Boer PT, Postma MJ, Pitman R. Retrospective public health impact of a quadrivalent influenza vaccine in the United States. Influenza Other Respir Virus 2015;9(Suppl 1):39–46.
[9] DiazGranados CA, Denis M, Plotkin S. Seasonal influenza vaccine efficacy and its determinants in children and non-elderly adults: a systematic review with meta-analyses of controlled trials. Vaccine 2012;31:49–57.
[10] Tricco AC, Chit A, Soobiah C, Hallett D, Meier G, Chen MH, et al. Comparing influenza vaccine efficacy against mismatched and matched strains: a systematic review and meta-analysis. BMC Med 2013;11:153.
[11] Levandowski RA, Regnery HL, Staton E, Burgess BG, Williams MS, Groothuis JR. Antibody responses to influenza B viruses in immunologically unprimed children. Pediatrics 1991;88:1031–6.
[12] Ambrose CS, Levin MJ. The rationale for quadrivalent influenza vaccines. Human Vacc Immunotherapeut 2012;8:81–8.
[13] Choi WS, Noh JY, Lee J, Choi JY, Lee JS, Kim MS, et al. Immunogenicity and safety of a split-virion quadrivalent influenza vaccine in adults 18-60 years of age in the Republic of Korea. Human Vacc Immunotherapeut; 2017 [Epub ahead of print].
[14] Lu CY, Ferracin C, Chiu CH, Lavis N, Huang CH, Huang LM. Immunogenicity and safety of a quadrivalent influenza vaccine in children and adolescents in Taiwan: a phase III open-label trial. Trials Vacc 2016;5:48–52.
[15] Pepin S, Szymanski H, Rochin Kobashi IA, Villagomez Martinez S, Gonzalez Zamora JF, Brzostek J, et al. Safety and immunogenicity of an intramuscular quadrivalent influenza vaccine in children 3 to 8 y of age: A phase III randomized controlled study. Human Vacc Immunotherapeut 2016;12:3072–8.
[16] Sesay S, Brzostek J, Meyer I, Donazzolo Y, Leroux-Roels G, Rouzier R, et al. Safety, immunogenicity, and lot-to-lot consistency of a split-virion quadrivalent influenza vaccine in younger and older adults: a phase III randomized, double-blind clinical trial. Human Vac Immunotherapeut; 2017 [Epub ahead of print].
[17] World Health Organization. Table 2a. TIV vaccination of children aged 6 months – 2 years. Geneva: WHO; 2012 [cited 22 Jun 2018]. <http://www.who.int/immunization/position_papers/influenza_grad_efficacy_age_2to24_months.pdf?ua=1>.
[18] Wright PF, Dolin R, La Montagne JR. From the national institute of allergy and infectious diseases of the national institutes of health, the center for disease control, and the bureau of biologics of the food and drug administration. summary of clinical trials of influenza vaccines–II. J Infect Dis 1976;134:633–8.
[19] Jain VK, Domachowske JB, Wang L, Ofori-Anyinam O, Rodriguez-Weber MA, Leonardi ML, et al. Time to change dosing of inactivated quadrivalent influenza vaccine in young children: evidence from a phase III, randomized, controlled trial. J Pediat Infect Dis Soc 2017;6:9–19.
[20] Langley JM, Vanderkooi OG, Garfield HA, Hebert J, Chandrasekaran V, Jain VK, et al. Immunogenicity and safety of 2 dose levels of a thimerosal-free trivalent seasonal influenza vaccine in children aged 6–35 months: a randomized, controlled trial. J Pediat Infect Dis Soc 2012;1:55–63.
[21] Skowronski DM, Hottes TS, Chong M, De Serres G, Scheifele DW, Ward BJ, et al. Randomized controlled trial of dose response to influenza vaccine in children aged 6 to 23 months. Pediatrics 2011;128:e276–89.
[22] Pepin S, Donazzolo Y, Jambrecina A, Salamand C, Saville M. Safety and immunogenicity of a quadrivalent inactivated influenza vaccine in adults. Vaccine 2013;31:5572–8.
[23] SAGE Working Group. Background paper on influenza vaccines and immunization. Geneva: WHO; 2012 [cited 22 Jun 2018]. <http://www.who.int/immunization/sage/meetings/2012/april/1_Background_Paper_Mar26_v13_cleaned.pdf>.
[24] Claeys C, Dbaibo G, Izu A, Kosalaraksa P, Rivera L, Schuind A, et al. Inactivated quadrivalent influenza vaccine prevents disease due to matched and mismatched strains: a randomised trial in children aged 6-35 months during 2011–2014. In: Poster ESP17-0408. 35th annual meeting of the European society for pediatric infectious diseases. Madrid, Spain; 2017.
[25] Pavia-Ruz N, Angel Rodriguez Weber M, Lau YL, Nelson EA, Kerdpanich A, Huang LM, et al. A randomized controlled study to evaluate the immunogenicity of a trivalent inactivated seasonal influenza vaccine at two dosages in children 6 to 35 months of age. Human Vacc Immunotherapeut 2013;9:1978–88.
[26] Cox RJ. Correlates of protection to influenza virus, where do we go from here? Human Vacc Immunotherapeut 2013;9:405–8.
[27] Ohmit SE, Petrie JG, Cross RT, Johnson E, Monto AS. Influenza hemagglutination-inhibition antibody titer as a correlate of vaccine-induced protection. J Infect Dis 2011;204:1879–85.
[28] Cadorna-Carlos JB, Nolan T, Borja-Tabora CF, Santos J, Montalban MC, de Looze FJ, et al. Safety, immunogenicity, and lot-to-lot consistency of a quadrivalent inactivated influenza vaccine in children, adolescents, and adults: a randomized, controlled, phase III trial. Vaccine 2015;33:2485–92.
[29] Smith NM, Bresee JS, Shay DK, Uyeki TM, Cox NJ, Strikas RA. Prevention and control of influenza: recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR Recommend Rep: Morbid Mort Weekly Rep Recommend Rep 2006;55:1–42.