Supplementary material

Prevention of influenza across diverse geographic regions during five influenza seasons: a randomized clinical trial of inactivated quadrivalent influenza vaccine

G Dbaibo et al for the Flu4VEC Study Group

# Study group

The inFLUenza 4 (quadrivalent) Vaccine Efficacy in Children (Flu4VEC) study group comprises:

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# Methods

## Ethics approval

The study was funded by GlaxoSmithKline Biologicals SA and registered with ClinicalTrials.gov (NCT01439360). It was approved by independent ethics committees or institutional review boards, conducted in accordance with the Declaration of Helsinki, the International Conference on Harmonisation Good Clinical Practice (ICH-GCP) guidelines, and regulatory requirements of participating countries. Parents or legally acceptable representatives provided written informed consent.

## Study vaccines

The IIV4 was manufactured by GSK, Dresden, Germany and contained 15 µg hemagglutinin antigen per strain per 0.5 mL dose, with strain composition according to WHO seasonal recommendations. Vaccine-primed children received a single intramuscular dose on Day 0; vaccine-unprimed children received two doses on Days 0 and 28. Most (99%) were unprimed for influenza vaccination i.e. they had not previously received at least two doses of seasonal influenza vaccine separated by at least 28 days.

Three possible control vaccines were used in the study: hepatitis A vaccine, varicella vaccine or pneumococcal conjugate vaccine (PCV), based on age and vaccine-priming status.

## Recording of symptoms and healthcare utilization

For influenza-like illness (ILI) and lower respiratory infection (LRI), parents recorded temperature and symptoms of cough, runny nose/nasal congestion, vomiting and feeling unwell; symptom severity was rated as none, minor, moderate or major. For acute otitis media (AOM), parents recorded temperature and symptoms of ear tugging or holding ear, increased crying, fussiness, disturbed sleep, decreased play and eating less; symptom severity was rated as none, a little or a lot using the AOM-severity of symptoms scale.

Healthcare utilization was recorded by study staff at the end of the episode as: general practitioner or pediatrician visit; medical specialist visit; emergency room visit; hospitalization, including intensive care unit admissions; use of supplementary oxygen therapy for >8 hours). Absenteeism was recorded as the number of missed day-care days for the child and missed days of paid work for the parents if applicable.

## Study endpoints

The two primary endpoints of the overall study were vaccine efficacy against the first occurrence of RT-PCR-confirmed moderate-to-severe influenza or any influenza (regardless of disease severity) in the entire study cohort. The secondary endpoints of the overall study were vaccine efficacy against the following: lower respiratory infection associated with RT-PCR-confirmed influenza; moderate-to-severe culture-confirmed influenza associated with antigenically-matching strains; all culture-confirmed influenza associated with antigenically-matching strains; moderate-to-severe culture-confirmed influenza associated with any seasonal strain; all culture-confirmed influenza associated with any seasonal strain; acute otitis media associated with RT-PCR-confirmed influenza; severe RT-PCR-confirmed influenza. These endpoints were also evaluated in the present analysis by seasonal cohort.

Table S1. Baseline demographics by region (total vaccinated cohort)

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
|  | **Europe/Lebanon/Turkey** | | **Asia Pacific** | | **Central America** | |
|  | **IIV4 N=1672** | **Control N=1669** | **IIV4 N=2711** | **Control N=2711** | **IIV4 N=1623** | **Control N=1632** |
| **Age at first vaccination, months** |  |  |  |  |  |  |
| Median (range) | 20.0 (6, 35) | 20.0 (6, 35) | 25.0 (6, 35) | 25.0 (6, 43) | 19.0 (6, 35) | 19.0 (6, 35) |
| **Female, n (%)** | 813 (48.6) | 793 (47.5) | 1326 (48.9) | 1349 (49.8) | 794 (48.9) | 783 (48.0) |
| **Geographic ancestry, n (%)** |  |  |  |  |  |  |
| South East Asian | 1 (0.1) | 2 (0.1) | 1660 (61.2) | 1664 (61.4) | 0 | 0 |
| Central or South Asian | 16 (1.0) | 7 (0.4) | 1046 (38.6) | 1046 (38.6) | 0 | 0 |
| Other Asian | 1 (0.1) | 0 | 3 (0.1) | 0 | 0 | 0 |
| White, Caucasian/European heritage | 1471 (88.0) | 1481 (88.7) | 0 | 0 | 0 | 1 (0.1) |
| White, Arabic/North African heritage | 142 (8.5) | 149 (8.9) | 0 | 0 | 0 | 0 |
| African/African American heritage | 20 (1.2) | 17 (1.0) | 0 | 0 | 4 (0.2) | 3 (0.2) |
| Native Hawaiian or other Pacific Islander | 0 | 0 | 1 (0.0) | 0 | 2 (0.1) | 0 |
| American Indian or Alaskan Native | 0 | 0 | 0 | 0 | 0 | 0 |
| Other\* | 21 (1.3) | 13 (0.8) | 1 (0.0) | 1 (0.0) | 1617 (99.6) | 1628 (99.8) |

\*Mainly mixed race or Hispanic origin  
IIV4: inactivated quadrivalent influenza vaccine

Table S2. Vaccine efficacy against the secondary endpoints of the study (total vaccinated cohort, time-to-event analysis)

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
|  | **IIV4** | | **Control** | | **Vaccine efficacy, % (95% CI)** |
|  | **n** | **Attack rate, %** | **n** | **Attack rate, %** |  |
| LRI associated with RT-PCR-confirmed influenza | | | | | |
| Cohort 1 | 9 | 1.02 | 12 | 1.34 | 22.8 (-82.3, 68.5) |
| Cohort 2 | 0 | 0.00 | 2 | 0.16 | 100 (-64.3, -) |
| Cohort 3 | 4 | 0.51 | 20 | 2.58 | 80.0 (47.3, 94.2) |
| Cohort 4 | 8 | 1.07 | 13 | 1.73 | 38.3 (-46.3, 75.6) |
| Cohort 5 | 7 | 0.30 | 15 | 0.64 | 54.2 (-8.5, 82.5) |
| Moderate-to-severe culture-confirmed influenza associated with antigenically-matching strains | | | | | |
| Cohort 1 | 0 | 0.00 | 0 | 0.00 | - |
| Cohort 2 | 4 | 0.32 | 16 | 1.26 | 74.6 (30.7, 92.7) |
| Cohort 3 | 6 | 0.76 | 40 | 5.15 | 85.3 (67.9, 94.4) |
| Cohort 4 | 3 | 0.40 | 6 | 0.80 | 50.7 (-87.0, 89.6) |
| Cohort 5 | 7 | 0.30 | 27 | 1.16 | 74.3 (44.2, 89.7) |
| All culture-confirmed influenza associated with antigenically-matching strains | | | | | |
| Cohort 1 | 0 | 0.00 | 1 | 0.11 | 100 (-460.4, -) |
| Cohort 2 | 21 | 1.67 | 48 | 3.79 | 55.8 (27.3, 74.1) |
| Cohort 3 | 18 | 2.28 | 73 | 9.41 | 76.3 (61.2, 86.3) |
| Cohort 4 | 13 | 1.73 | 19 | 2.53 | 33.0 (-34.5, 67.7) |
| Cohort 5 | 37 | 1.59 | 77 | 3.31 | 52.8 (30.7, 68.5) |
| Moderate-to-severe culture-confirmed influenza associated with any seasonal strain | | | | | |
| Cohort 1 | 22 | 2.49 | 37 | 4.14 | 39.3 (-1.9, 64.8) |
| Cohort 2 | 8 | 0.63 | 23 | 1.82 | 64.7 (24.4, 85.2) |
| Cohort 3 | 8 | 1.02 | 54 | 6.96 | 85.6 (71.5, 93.7) |
| Cohort 4 | 12 | 1.60 | 27 | 3.60 | 56.4 (16.0, 78.7) |
| Cohort 5 | 30 | 1.29 | 81 | 3.48 | 63.6 (45.3, 76.4) |
| All culture-confirmed influenza associated with any seasonal strain | | | | | |
| Cohort 1 | 40 | 4.52 | 91 | 10.19 | 56.7 (37.8, 70.5) |
| Cohort 2 | 30 | 2.38 | 71 | 5.61 | 57.5 (35.6, 72.7) |
| Cohort 3 | 29 | 3.68 | 113 | 14.56 | 75.9 (64.3, 84.2) |
| Cohort 4 | 60 | 7.99 | 83 | 11.07 | 30.2 (3.0, 50.1) |
| Cohort 5 | 152 | 6.54 | 257 | 11.04 | 42.7 (30.0, 53.2) |
| AOM associated with RT-PCR-confirmed influenza | | | | | |
| Cohort 1 | 6 | 0.68 | 12 | 1.34 | 47.8 (-34.5, 81.8) |
| Cohort 2 | 1 | 0.08 | 0 | 0.00 | -8.27E9 (-, 82.4) |
| Cohort 3 | 1 | 0.13 | 10 | 1.29 | 90.0 (47.7, 99.5) |
| Cohort 4 | 0 | 0.00 | 1 | 0.13 | 100 (-471.9, -) |
| Cohort 5 | 4 | 0.17 | 5 | 0.21 | 19.1 (-205.6, 80.0) |
| Severe RT-PCR-confirmed influenza | | | | | |
| Cohort 1 | 0 | 0.00 | 0 | 0.00 | - |
| Cohort 2 | 0 | 0.00 | 0 | 0.00 | - |
| Cohort 3 | 0 | 0.00 | 0 | 0.00 | - |
| Cohort 4 | 1 | 0.13 | 0 | 0.00 | -2.88E9 (-, 83.2) |
| Cohort 5 | 1 | 0.04 | 3 | 0.13 | 66.9 (-158.3, 98.4) |

n: number of children with a case

AOM: acute otitis media; CI: confidence interval; LRI: lower respiratory infection; IIV4: inactivated quadrivalent influenza vaccine; RT-PCR: reverse transcription polymerase chain reaction; TVC: total vaccinated cohort

Figure S1. Incidence and vaccine efficacy against culture-confirmed influenza of any severity according to vaccine-matched or -mismatched antigenic characterization (total vaccinated cohort)









CI: confidence interval; ND: not determined; VE: vaccine efficacy