Efficacy of Inactivated Split-Virus Influenza Vaccine against Culture-Confirmed Influenza in Healthy Adults: A Prospective, Randomized, Placebo-Controlled Trial

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Background. A new trivalent inactivated split-virus influenza vaccine (TIV) was recently introduced in the United States. We assessed the efficacy of TIV against culture-confirmed influenza A and/or B.

Methods. In this double-blind trial conducted from September 2006 to May 2007 in the Czech Republic and Finland, participants aged 18–64 years were randomized to receive 1 dose of TIV (n = 5103) or placebo (n = 2549). Influenza-like illnesses (ILI) (defined as at least 1 systemic symptom [fever [oral temperature, ≥37.8°C] and/or myalgia] and at least 1 respiratory symptom [cough and/or sore throat]) were identified by both active (biweekly phone contact) and passive surveillance. Nasal and throat swab specimens were collected for viral culture.

Results. The attack rate for culture-confirmed ILI was 3.2% in the placebo group, with most strains identified as influenza A (all except 1 were H3N2) matching the vaccine strain. There were 6 cases of influenza B, all of which were of a different lineage (Yamagata) than the vaccine strain. Vaccine efficacy against culture-confirmed influenza A and/or B due to strains antigenically matched to the vaccine was 66.9% (95% confidence interval [CI], 51.9%–77.4%; P < .001) and to any strain was 61.6% (95% CI, 46.0%–72.8%; P < .001).

Conclusion. TIV is efficacious against culture-confirmed influenza in healthy adults.

Trial Registration. ClinicalTrials.gov identifier: NCT00363870.

Each year, trivalent influenza vaccines are produced that contain the 3 strains (2 influenza A and 1 influenza B) predicted by the World Health Organization (WHO) to be the predominant circulating strains for the next influenza season [1, 2]. A trivalent inactivated split-virus influenza vaccine (TIV) manufactured by GlaxoSmithKline (GSK) Biologicals in embryonated eggs has been available in several countries since 1987 but was only recently approved for use in the United States [3, 4, 5].

A first efficacy study of this vaccine was conducted among healthy adults during the 2005–2006 influenza season in the Czech Republic [6]. It was a prospective, randomized, placebo-controlled design with both active and passive surveillance for influenza-like illness (ILI) and used the criterion standard end point of culture confirmation of influenza virus infection. The definition of ILI (the presence of fever plus either cough or...
sore throat) was based on that used by the Centers for Disease Control and Prevention (CDC) [7]. The study was powered on the basis of the assumption that the attack rate of culture-confirmed influenza in the placebo group would be 4%. However, the actual attack rate was much lower (0.9%), so the study lacked the power to demonstrate efficacy [6]. Furthermore, the majority of the cases were influenza B cases, which were found to have been caused by a strain of a different lineage than the vaccine strain [6].

We undertook a second prospective, randomized, placebo-controlled, efficacy study of TIV among healthy adults during the 2006–2007 influenza season. The same method was used but with the following refinements: the sample size was based on the assumption of a lower attack rate; to increase case capture, a less stringent case definition of ILI was used than in the previous study; and efficacy against culture-confirmed influenza for strains antigenically matched to the vaccine was specified as the primary objective.

METHODS

Study design and objectives. This was a randomized, double-blind, placebo-controlled study conducted during the 2006–2007 influenza season at 15 centers located in the Czech Republic and Finland. The protocol and study documents were approved by the ethics committees of each country.

The primary objective was to evaluate the efficacy of TIV versus placebo in the prevention of culture-confirmed influenza A and/or B due to strains antigenically matched to the vaccine. Secondary efficacy objectives included the evaluation of (1) TIV in the prevention of culture-confirmed influenza due to strains antigenically matched to the vaccine for each of 2 vaccine lots, (2) TIV in the prevention of culture-confirmed influenza A and/or B attributable to any influenza A or B strain, and (3) TIV in the prevention of ILI. Other secondary objectives were the assessment of safety and, in a subset of subjects, the assessment of vaccine reactogenicity and immunogenicity.

Participants. Eligible participants were self-referred women or men who were between 18 and 64 years of age, had no significant clinical disease at the time of vaccination, and provided written informed consent. Blinding to treatment assignment was maintained until study analysis.

Vaccination and blood sampling. Participants were randomized to receive 1 dose of TIV (lot 1 or lot 2 of Fluarix) or placebo (normal saline solution) at the first study visit (day 0) by intramuscular injection. Each 0.5-ml dose of TIV contained 15 μg of each of the hemagglutinin antigens of strains A/New Caledonia/20/99(H1N1) IVR-116, A/Wisconsin/67/2005(H3N2), and B/Malaysia/2506/2004 (from the Victoria lineage).

Blood samples for the evaluation of influenza vaccine immunogenicity were obtained from the randomly selected, planned subset of ~500 participants just prior to vaccination and 21–28 days later.

Case definitions. Culture-confirmed influenza A and/or B due to strains antigenically matched to the vaccine (primary end point) was defined as an episode of ILI occurring after administration of the study vaccine or placebo for which a nasal or throat swab specimen yielded influenza virus A and/or B in cell culture. The virus isolate was classified as matching the vaccine A and/or B strains on the basis of its reaction with influenza strain–typing reagents (see the section on laboratory assays below).

ILI (a secondary end point and the trigger to collect a specimen for influenza virus detection) was defined as at least 1 systemic symptom (fever [oral temperature, ≥37.8°C] and/or myalgia) and at least 1 respiratory symptom (cough and/or sore throat). An ILI episode was defined as the period from the first day of ILI symptoms to the last day of ILI symptoms. A new episode was considered to have occurred only after the complete resolution of the previous one.

Surveillance and follow-up. From the day of vaccination, all subjects were instructed to report any ILI symptoms to the investigator (passive surveillance for ILI). Active surveillance (biweekly phone contact) for ILI was conducted from 2 weeks after vaccination to the beginning of May 2007.

For each case of suspected ILI, a nasal and throat swab specimen (composed of a swab of both nasal sinuses and a second swab of the throat) was collected for culture (as much as possible on the same day as the ILI report and, at the latest, 5 days after the ILI onset). Each subject was provided with a calibrated thermometer to measure temperature and a diary card to record temperatures and symptoms during the ILI episode.

Laboratory assays. The nasal and throat specimens were stored at −70°C and transferred to Quest Diagnostic Clinical Trials Laboratory (Heston, Middlesex, UK) for conventional influenza virus culture in Madin Darby Canine Kidney and Rhesus Monkey Kidney cells. Cultures were determined to be positive for influenza virus on the basis of cytopathic effect, and identification as either influenza A or influenza B was based on immunofluorescence staining. Frozen aliquots of culture supernatants from positive viral cultures were sent to J. Treanor’s laboratory (University of Rochester Vaccine Evaluation Unit Influenza Serology Laboratory, Rochester, New York) for identification of virus-matching isolates by conventional hemagglutination-inhibition testing (using H1 and H3 antisera from the CDC and B/Malaysia antiserum from the WHO).

Serum samples were stored at −20°C until blinded analyses were conducted at GSK Biologicals in Dresden, Germany. All samples were tested in a validated microtiter hemagglutination-inhibition test using chicken erythrocytes, with the 3 virus strains present in the TIV used as antigens, as described elsewhere [5].
Figure 1. Trial profile.

Total Enrolled N = 7652
Total Vaccinated N = 7652
Intention-to-treat Cohort for Efficacy and Safety

Placebo N = 2549
Intention-to-treat Cohort for Efficacy and Safety

Placebo N = 2527
Per-protocol Efficacy Cohort Influenza Season
- Administration of vaccines forbidden in the protocol: 1 subject
- Administration of medication forbidden in the protocol: 5 subjects
- Underlying medical condition forbidden by the protocol: 8 subjects
- Subjects not exposed during the influenza season: 8 subjects

Vaccine N = 5103
Intention-to-treat Cohort for Efficacy and Safety

Vaccine N = 5050
Per-protocol Efficacy Cohort Influenza Season
- Administration of vaccines forbidden in the protocol: 4 subjects
- Administration of medication forbidden in the protocol: 6 subjects
- Randomization code broken at investigator site: 2 subjects
- Protocol violation (inclusion/exclusion criteria): 1 subject
- Underlying medical condition forbidden by the protocol: 15 subjects
- Subjects not exposed during the influenza season: 25 subjects

N = 460
Intention-to-treat Cohort Subset

Placebo N = 155
Intention-to-treat Cohort Reactogenicity Subset

Placebo N = 148
Per-protocol Cohort Immunogenicity Subset
- Administration of medication forbidden in the protocol: 1 subject
- Underlying medical condition forbidden by the protocol: 1 subject
- Non compliance with blood sampling: 4 subjects
- Essential serological data missing: 1 subject

Vaccine N = 305
Intention-to-treat Cohort Reactogenicity Subset

Vaccine N = 291
Per-protocol Cohort Immunogenicity Subset
- Protocol violation (inclusion/exclusion criteria): 1 subject
- Underlying medical condition forbidden by the protocol: 1 subject
- Non compliance with blood sampling: 10 subjects
- Essential serological data missing: 2 subjects
Figure 2. A, Distribution of influenza-like illness (ILI) episodes (n = 1205) per study month. B, Distribution of culture-confirmed influenza (CCI) cases for any strain (n = 145) and for strains antigenically matched to the vaccine (n = 123) per study month.

Statistical analysis. On the basis of an attack rate of 2% in the placebo group for culture-confirmed influenza (type A and/or B) cases for strains antigenically matched to the vaccine (primary end point), it was estimated that a total of 77 cases (7218 total evaluable subjects) were needed to demonstrate with at least 90% power that the lower limit of the 95% confidence interval (CI) for the vaccine efficacy (VE) was >35%, assuming a VE of 70% with α = 0.025 (1-sided).

VE against the primary and secondary end points was estimated as 1 minus the relative risk of the event of interest among the TIV group versus the placebo group. The 95% CIs for VE were calculated using a conditional exact method. The attack rates in each treatment group were compared using the Fisher exact test.

The primary analysis of VE was performed in the intention-to-treat (total vaccinated) cohort for efficacy over the whole study period. Efficacy against ILI was also assessed in the per-protocol cohort for efficacy in the influenza season (Figure 2A).

The influenza season was defined on a country-by-country basis as the period beginning on the Monday of the first week with 2 culture-confirmed influenza cases reported in the study and ending on the Sunday of the week with the last culture-confirmed case reported in the study.

RESULTS

Participants. All enrolled subjects were vaccinated. The intention-to-treat cohort for efficacy and safety (n = 7652) included 5103 subjects vaccinated with TIV (2 different lots) and 2549 subjects vaccinated with placebo (Figure 1). The demographic profiles of the TIV and placebo groups were comparable with respect to age (mean ± standard deviation, 40.0 ± 13.3 and 39.7 ± 13.3 years, respectively) and gender and racial distribution (60% female and 99.9% white in both groups). Approximately 75% of subjects in both study groups had no history of influenza vaccination within the last 3 influenza sea-
sions before enrollment. Most subjects (98%) were followed up until the end of the influenza season.

**Overview of influenza cases.** During surveillance (September 2006 to May 2007), ILI was reported by 1052 of 7652 subjects. Some subjects had >1 episode of ILI, and the total number of ILI episodes was 1205. As illustrated in Figure 2A, the number of ILI episodes peaked in February 2007. Nasal and throat specimens were collected for 1151 (95.6%) of the ILI episodes. There were 145 subjects with ILI who had culture-confirmed influenza A and/or B; of these, 123 subjects had disease due to strains antigenically matched to the vaccine. The majority (>95%) of culture-confirmed cases occurred between January and March 2007 (Figure 2B). As shown in Table 1, most culture-confirmed cases (95%) in both groups were identified as H3N2 influenza A. Most cases (84.8%) were typed as antigenically matched to the vaccine’s influenza A/Wisconsin/67/2005(H3N2) strain. Only 1 case of H1 influenza A was identified, but it was not antigenically matched to the vaccine’s A/New Caledonia/20/99(H1N1) strain. There were 3 cases of influenza B in each group, which were all from the Yamagata lineage [8] and therefore not antigenically matched to the vaccine’s B/Malaysia/2506/2004 strain from the Victoria lineage [8].

Approximately 50% of the culture-confirmed cases in both groups and 28.8% (TIV) and 36.4% (placebo) of ILI episodes presented with a combination of all 4 ILI symptoms (fever, myalgia, cough, and sore throat). The presence of at least fever in culture-confirmed influenza cases (TIV, 90.5%; placebo, 92.7%) tended to be more common than in ILI episodes (TIV, 66.5%; placebo, 72.5%). The presence of at least cough in culture-confirmed cases (TIV, 96.8%; placebo, 96.3%) also tended to be more common than in ILI episodes (TIV, 79.9%; placebo, 84.3%).

The majority of nasal and throat specimens were collected by day 2 after ILI onset (Figure 3), with a mean time period of 1.7 days after ILI onset in both groups.

**Efficacy.** The primary objective of the study was met because statistically significant VE for TIV (66.9%; P<.001) was demonstrated against culture-confirmed influenza A and/or B due to strains antigenically matched to the vaccine, with a lower CI limit (51.9%) >35% (Table 2). The estimates of VE were consistent for the 2 lots of TIV administered (Table 2). Statistically significant VE was also demonstrated against culture-confirmed influenza A and/or B due to any influenza strain (61.6%; P<.001) (Table 2), although there were only a limited number of cases attributable to drift strains detected. Statistically significant efficacy was demonstrated against ILI in both the intention-to-treat cohort (17.9%; P<.001) and specifically during the influenza season in the per-protocol cohort for efficacy (25.6%; P<.001). In contrast to culture-confirmed influenza, the estimates of efficacy against ILI tended to increase for those cases in which fever was present with or without myalgia (27.1% and 38.3%, respectively; P<.001). No evidence of efficacy against ILI was found before the start of the influenza season (3.9%; P = 0.688).

We performed a preliminary assessment of the effect of vaccination in older subjects aged 50–64 years. The majority of influenza cases occurred in the <50-year-old group (who made up ~70% of the study population), for whom the attack rate in the placebo group was 3.6%, whereas for those aged 50–64 years the attack rate in the placebo group was 1.1%. Although there were too few cases in the 50–64-year-old group to calculate VE by standard statistical methods, a trend toward a lower VE was observed.

**Immunogenicity.** Table 3 demonstrates that TIV elicited a

<table>
<thead>
<tr>
<th>Antigen-type match to vaccine strain</th>
<th>TIV (n = 5103)</th>
<th>Placebo (n = 2549)</th>
<th>All (n = 7652)</th>
</tr>
</thead>
<tbody>
<tr>
<td>H1 Influenza A</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Matched</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Nonmatched</td>
<td>0 (0)</td>
<td>1 (1.2)</td>
<td>1 (0.7)</td>
</tr>
<tr>
<td>Untyped</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>H3 Influenza A</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Matched</td>
<td>49 (77.8)</td>
<td>74 (90.2)</td>
<td>123 (84.8)</td>
</tr>
<tr>
<td>Nonmatched</td>
<td>8 (12.7)</td>
<td>3 (3.7)</td>
<td>11 (7.6)</td>
</tr>
<tr>
<td>Untyped</td>
<td>3 (4.8)</td>
<td>1 (1.2)</td>
<td>4 (2.8)</td>
</tr>
<tr>
<td>Influenza B</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Matched</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Nonmatched</td>
<td>3 (4.8)</td>
<td>3 (3.7)</td>
<td>6 (4.1)</td>
</tr>
<tr>
<td>Untyped</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Total</td>
<td>63 (100)</td>
<td>82 (100)</td>
<td>145 (100)</td>
</tr>
</tbody>
</table>

**NOTE.** Data are no. (%) of subjects. TIV, trivalent inactivated split-virus influenza vaccine.
Figure 3. Number of influenza-like illness (ILI) episodes (A) and culture-confirmed influenza (CCI) cases for any strain (B), stratified by the time period between onset of ILI and collection of nasal and throat swab specimens.

strong antibody response (as assessed by hemagglutination-inhibition assay) against all 3 vaccine strains. The responses exceeded the acceptability criteria of both the Center for Biologics Evaluation and Research (CBER) [9] and the Committee for Medicinal Products for Human Use (CHMP) [10].

DISCUSSION

Our study demonstrates that, among adults 18–64 years of age, the TIV evaluated is efficacious against culture-confirmed influenza A and/or B, as well as against clinical cases of ILI. The TIV that was evaluated elicited a strong humoral immune response that exceeded both CBER and CHMP acceptability criteria [9, 10]. However, the possible relationship between a postvaccination hemagglutination-inhibition antibody level and protection from disease could not be deduced by this study because postvaccination blood specimens were collected from only a subset of participants.

Despite publication of a large number of studies of the effectiveness or efficacy of influenza vaccines, the evidence supporting the clinical benefit of a number of marketed TIVs is limited, because many studies were either nonrandomized (chiefly cohort studies) and/or conducted among a small number of volunteers [11]. Moreover, clinical diagnosis of influenza is known to be of low specificity and hence does not offer an accurate means to estimate a vaccine’s protective efficacy; laboratory confirmation by detection of virus is essential to overcome nonspecificity and ascertainment bias [12–16].

Our study was designed to overcome these design limitations: it was a placebo-controlled and randomized study with influenza cases confirmed by virus culture. To allow generalization

Table 2. Attack Rates and Vaccine Efficacies against Influenza (Intention-to-Treat Cohort)

<table>
<thead>
<tr>
<th>Event, group</th>
<th>Proportion with Eventb</th>
<th>No. of events in each group</th>
<th>% (95% CI)</th>
<th>Attack rate</th>
<th>Vaccine efficacy</th>
<th>P&lt;sup&gt;c&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Influenza due to antigenically matched strains (primary objective)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TIV</td>
<td>49/5103</td>
<td>49</td>
<td>1.0 (0.7–1.3)</td>
<td>66.9 (51.9–77.4)</td>
<td>&lt;.001</td>
<td></td>
</tr>
<tr>
<td>Placebo</td>
<td>74/2549</td>
<td>74</td>
<td>2.9 (2.3–3.6)</td>
<td>…</td>
<td>…</td>
<td>…</td>
</tr>
<tr>
<td>Influenza due to antigenically matched strains by vaccine lot</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TIV lot 1</td>
<td>25/2553</td>
<td>25</td>
<td>1.0 (0.6–1.4)</td>
<td>66.3 (46.3–79.5)</td>
<td>&lt;.001</td>
<td></td>
</tr>
<tr>
<td>TIV lot 2</td>
<td>24/2550</td>
<td>24</td>
<td>0.9 (0.6–1.4)</td>
<td>67.6 (48.0–80.4)</td>
<td>&lt;.001</td>
<td></td>
</tr>
<tr>
<td>Placebo</td>
<td>74/2549</td>
<td>74</td>
<td>2.9 (2.3–3.6)</td>
<td>…</td>
<td>…</td>
<td>…</td>
</tr>
<tr>
<td>Influenza due to any strain</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TIV</td>
<td>63/5103</td>
<td>63</td>
<td>1.2 (0.9–1.6)</td>
<td>61.6 (46.0–72.8)</td>
<td>&lt;.001</td>
<td></td>
</tr>
<tr>
<td>Placebo</td>
<td>82/2549</td>
<td>82</td>
<td>3.2 (2.6–4.0)</td>
<td>…</td>
<td>…</td>
<td>…</td>
</tr>
</tbody>
</table>

NOTE. Vaccine efficacy was calculated with the conditional exact method. CI, confidence interval; TIV, trivalent inactivated split-virus influenza vaccine.

* Indicated are culture-confirmed episodes of influenza A and/or B due to strains antigenically matched to the vaccine or due to any strain.

b No. of subjects reporting at least 1 event in each group per the total number of subjects in each group.

c Calculated using the 2-sided Fisher exact test.
Table 3. Hemagglutination-Inhibition Antibody Response Before (Day 0) and 21 Days After (Day 21) Vaccination (Per-Protocol Cohort Subset for Immunogenicity)

<table>
<thead>
<tr>
<th>Antibody response</th>
<th>Acceptance criteria</th>
<th>Influenza A</th>
<th>Influenza B/Malaysia/2506/2004</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>TIV (n = 291)</td>
<td>Placebo (n = 148)</td>
</tr>
<tr>
<td>Geometric mean titer</td>
<td>CHMP&lt;sup&gt;a&lt;/sup&gt;</td>
<td>27.0 (22.8–32.0)</td>
<td>29.8 (23.1–38.4)</td>
</tr>
<tr>
<td>Day 0</td>
<td>No standard</td>
<td>27.0 (22.8–32.0)</td>
<td>29.8 (23.1–38.4)</td>
</tr>
<tr>
<td>Day 21</td>
<td>No standard</td>
<td>541.0 (451.0–649.0)</td>
<td>34.7 (27.2–44.4)</td>
</tr>
<tr>
<td>Seroconversion factor or geometric mean ratio&lt;sup&gt;c&lt;/sup&gt;</td>
<td>&gt;2.5</td>
<td>20.0 (16.2–24.7)</td>
<td>1.2 (1.1–1.3)</td>
</tr>
<tr>
<td>Seroconversion rate or significant increase in titer, &lt;sup&gt;d&lt;/sup&gt; %</td>
<td>&gt;40 LL of 95% CI ≥ 40%</td>
<td>76.3 (71.0–81.1)</td>
<td>1.4 (0.2–4.8)</td>
</tr>
<tr>
<td>Seroprotection (titer/1:40), %</td>
<td>&gt;70 LL of 95% CI ≥70%</td>
<td>97.6 (95.1–99.0)</td>
<td>44.6 (36.4–53.0)</td>
</tr>
</tbody>
</table>

NOTE. Data in parentheses are 95% confidence intervals (CIs). CBER, US Center for Biologics Evaluation and Research; CHMP, European Union Committee for Medicinal Products for Human Use; LL, lower level.

<sup>a</sup> Criteria for hemagglutination-inhibition antibody response in 18-60-year-olds.

<sup>b</sup> Criteria for hemagglutination-inhibition antibody response in adults ≥65 years old.

<sup>c</sup> Data are the ratios of the geometric mean titers on day 21 to those on day 0.

<sup>d</sup> Seroconversion rate for hemagglutination-inhibition antibody response is defined as the percentage of vaccinated patients who have a prevaccination titer <1:10 and a postvaccination titer ≥1:40; a significant increase in antibody titer is defined as the percentage of vaccinated patients who have a prevaccination titer ≥1:10 and at least a 4-fold increase in postvaccination titer.
of results from season to season, all virus isolates were typed as matching the vaccine strain or not. We used passive and active surveillance (biweekly contact) to detect ILI cases, and because 98% of the subjects remained in follow-up from vaccination until the end of the influenza season, the conditions for case capture were optimal. For the majority of ILI episodes, the nasal and throat swab specimen was collected by day 2 after onset. Timely collection of specimens is important because viral shedding peaks during the first 24–72 h of illness [17].

Although the culture-confirmed placebo attack rate (3.2%) in this study was higher than that in our previous study [6], it was still at the lower end of the range (1.4%–16%) published for placebo groups in other randomized studies of healthy adults with laboratory-confirmed end points found in the Cochrane database [18].

The importance of factoring low attack rates into the study design has been illustrated by 2 studies of inactivated vaccine conducted over 2 consecutive influenza seasons. In an adult population aged 18–48 years in Michigan, VE for inactivated influenza vaccine against culture-confirmed influenza was estimated to be 77% (95% CI, 37%–92%) in the first season when the placebo attack rate was 5.8% but only 23% (95% CI, 153% to 73%) in the following season, when the attack rate was 1.8% [18, 19]. In the first season of a study conducted among children in Pittsburgh, Pennsylvania, when the attack rate for culture-confirmed influenza was 15.9% in the placebo group, VE was estimated to be 65% [95% CI, 4%–82%], whereas in the second season, when the attack rate was 3.3%, VE was negative [21]. Despite the relatively low attack rate in our study, we demonstrated statistically significant (P < .001) VE for the TIV evaluated against culture-confirmed influenza for antigenically matched strains in the vaccine (66.9% [95% CI, 51.9%–77.4%]) and any strain (61.6% [95% CI, 46.0%–72.8%]).

Apart from the studies described above [19, 20, 21], viral culture as the sole method for laboratory confirmation of cases has rarely been used as an efficacy end point for inactivated influenza vaccines. Most studies have used laboratory confirmation by serological analysis or a mixture of serological testing and culture. Serological analysis of acute-phase and convalescent-phase serum samples can, however, be confounded by the presence of vaccine-induced antibodies. In a recent review of Cochrane database studies involving healthy adults with laboratory end points, Jefferson et al [18] estimated that trivalent inactivated vaccines with content matching WHO recommendations were 80% efficacious against influenza when strain circulation was high. However, when data collected during the 1968–1969 pandemic were excluded, the estimate of 80% decreased to 73%. In the same review, the efficacy of parenteral nonpandemic influenza vaccines against ILI was found to be limited (16% in the best-case scenario). The clinical case definition of ILI used in the different studies was variable [18].

Our analysis of clinical symptoms in ILI and culture-confirmed cases indicated that fever and cough were the most pathognomonic symptoms for culture-confirmed influenza disease. The importance of fever as a positive predictor of influenza has also been reported by others [14, 15, 22]. We also observed that TIV tended to be more effective against ILI cases when fever was present (38.3% [95% CI, 25.8%–48.5%] during the influenza season) than against cases with fever OR myalgia (25.6% [95% CI, 12.8%–36.4%]). This illustrates further the potential bias of comparing VE data across studies when different case definitions were used.

Because this study was conducted using a wider age range (18–64 years) than other studies (which often just choose subjects up to 49 years of age), we attempted to assess the effect of vaccination in older subjects aged 50–64 years. Unfortunately, there were too few cases in this age group to draw conclusions on VE. Indeed, the attack rate for culture-confirmed influenza was much lower than that among those aged <50 years. The reason for the lower attack rate in the older population is not clear, but factors that may be responsible include lower exposure to disease, different susceptibility to disease, or lower sensitivity of the culture method in older subjects.

In conclusion, this study of healthy adults aged 18–64 years has shown that TIV, evaluated during a season (2006–2007) in which H3N2 viruses well matched to the vaccine strain predominated, was efficacious and offered clinical benefit that greatly exceeded risk.

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