THE ROYAL SOCIETY

doi 10.1098/rstb.2001.0982

Safety, efficacy and effectiveness of cold-adapted, live, attenuated, trivalent, intranasal influenza vaccine in adults and children

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Studies in children and adults revealed cold-adapted, live, attenuated, trivalent, intranasal influenza vaccine (CAIV-T) to be well accepted, well tolerated and highly protective against culture-confirmed influenza, and to provide significant health benefits. A 2 year, multicentre, double-blind, placebo-controlled efficacy field trial of CAIV-T in children aged 15–71 months with annual re-immunization revealed the vaccine to be highly protective against culture-confirmed influenza. Vaccine induced serum and secretory antibodies in vaccinated children. Overall, during 2 years of study, vaccine was 92% protective against culture-confirmed influenza. During the second year of study the vaccine was 86% protective against influenza A/Sydney/5/97-like virus, a significantly drifted strain not well matched to the vaccine. Antibody studies on children given CAIV-T revealed that high titres of cross-reacting antibodies to influenza A/Sydney/5/97 were induced with vaccination by live attenuated influenza A/Wuhan/359/95-like vaccine. Effectiveness measures revealed significant reductions in febrile illness (21% reduction in year 1, 19% reduction in year 2), febrile otitis media (33% reduction in year 1, 16% reduction in year 2) and associated antibiotic use among vaccinated children compared with placebo recipients. In adults, vaccination with CAIV-T resulted in protection during experimental challenge with virulent wild-type viruses. An effectiveness trial in adults demonstrated significant benefits of CAIV-T vaccine (28% reduction in days of missed work for febrile upper respiratory illness days with associated 45% reduction in days taking antibiotics). General use of CAIV-T has the potential to significantly reduce the impact of influenza in children and adults.

Keywords: intranasal influenza vaccine; influenza vaccine efficacy; influenza vaccine in children

1. INTRODUCTION

Despite availability of inactivated vaccine, influenza A and B remain significant causes of serious respiratory diseases. In adults, significant loss of work productivity is due to influenza. In children, significant secondary diseases including otitis media often accompany these common viral infections and viruses may be isolated from middle-ear fluid in some cases (Henderson *et al.* 1982; Chonmaitree *et al.* 1992; Heikkinen *et al.* 1999). The recent demonstrations that cold-adapted, live, attenuated, trivalent, intranasal influenza vaccine (CAIV-T) is safe and effective in children and adults represents a new opportunity to reduce the impact of influenza and to prevent its complications (Belshe *et al.* 1998, 2000*a*; Nichol *et al.* 1999). This paper reviews the results of recent clinical trials designed to measure efficacy and effectiveness in children and adults.

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2. VACCINE

CAIV-T was supplied by Aviron (Mountain View, CA, USA) and was frozen in single-dose intranasal applicators described below. The spray applicator consisted of a syringe-like device which was calibrated and divided for delivery of two 0.25 ml aliquots (one per nostril) as a large particle aerosol for a total delivered volume of 0.5 ml of study vaccine or placebo. The vaccine contained approximately $10^{7.0}$ 50% tissue culture-infective doses per dose of each of the three attenuated strains that matched the antigens as recommended for the trivalent inactivated influenza (TIV) vaccine by the US Food and Drug Administration for the 1996–1997 (A/Texas/36/91-like (H1N1), A/Wuhan 359/95 (H3N2) (a Nanchang-like virus) and B/Harbin/7/94-like viruses) and 1997–1998 (A/Shenzhen/227/95-like (H1N1), A/Wuhan/359/95 (H3N2) and B/Harbin/7/94-like) influenza seasons, respectively, for field trials (Belshe *et al.* 1998, 2000*a*; Nichol *et al.* 1999), and as described for adult challenge studies (Treanor *et al.* 1999). The vaccine was stored frozen at −20 °C or below.

3. STUDIES IN ADULTS

To assess vaccine efficacy (VE) in adults, challenge studies with virulent influenza viruses were conducted after vaccination of volunteers with either CAIV-T, TIV or placebo (Treanor *et al.* 1999). Virulent virus was given intranasally approximately 1 month after vaccine to evaluate the efficacy of vaccines.

To assess vaccine effectiveness in adults, 4561 working adults were randomized 2:1 to receive CAIV-T ($n=3041$) or placebo ($n=1520$) (Nichol *et al.* 1999). Data on adverse events during the 7 days following vaccination and on clinical outcomes for each month from November 1997 through to March 1998 were collected from diaries completed by the participants. Vaccine effectiveness was assessed for several illness syndromes during the peak and total outbreak periods (Nichol *et al.* 1999).

4. STUDIES IN CHILDREN

An efficacy field trial was conducted with CAIV-T in 1602 healthy children who were aged 15–71 months at the time of initial vaccination. Informed consent was obtained from a parent or guardian. Two doses of CAIV-T or placebo were given to the majority of children in year 1. In September of 1997, 1358 of the original study group of 1602 children (85%) were revaccinated with a single dose of CAIV-T or placebo by nasal spray.

The study was prospective, randomized, double-blind, placebo-controlled, and multicentre in design. The primary efficacy endpoint was the first episode of culture-confirmed influenza illness in each year. Details of the study design have been published (Belshe *et al.* 1998, 2000*a*).

H1N1 did not circulate during either of the 2 years of the pivotal efficacy field trial. Therefore, to develop surrogate data on VE against viral shedding, a subset of children were intranasally challenged with monovalent H1N1 vaccine strain 6 months after vaccination in the second year (Belshe *et al.* 2000*b*).

In a parallel study conducted at Vanderbilt University, 31 seronegative children aged 6–18 months were given the recommended two doses of TIV (Fluzone, split, Connaught Laboratories, Swiftwater, PA, USA) (Gruber *et al.* 1998). Pre- and post-vaccination sera from these children were used for the assessment of antibody responses to inactivated vaccine. For this comparison we tested sera from 25 children from the CAIV-T field trial who were initially seronegative for H3N2 and compared antibody responses stimulated by two doses of CAIV-T to the antibody responses in the cohort of children described above who received two doses of TIV (Gruber *et al.* 1998; Belshe & Gruber 2000).

5. RESULTS

(a) *Studies in adults*

A summary of the results of challenge studies in adults is shown in table 1. Placebo subjects had significantly more infection and illness than either vaccinated group. CAIV-T had 85% efficacy and TIV had 71% efficacy against infection and illness after experimental challenge with H1, H3 or B viruses (Treanor *et al.* 1999).

A summary of key effectiveness results in healthy working adults is shown in table 2. CAIV-T was safe and well tolerated. Vaccine significantly reduced the number of severe febrile illnesses and days of febrile upper respiratory tract illnesses among healthy, working adults (table 2). Vaccination also led to lower rates of work absenteeism, health-care provider visits, and the use of prescription antibiotics and non-prescription medications. These benefits were observed during a season in which the predominant circulating influenza virus strain, A/Sydney/05/97 (H3N2), was not well matched to strains contained in the vaccine (Nichol *et al.* 1999).

(b) *Studies in children*

No serious adverse events were associated with vaccination (Belshe *et al.* 1998, 2000*a*,*b*). Transient, minor symptoms of respiratory illness were present after dose 1 of year 1 when more vaccinated children, relative to placebo children, exhibited mild upper respiratory symptoms (rhinorrhoea or nasal congestion (on days 2, 3, 8, 9 post-vaccine), low grade fever (on day 2 post-vaccine) or decreased activity (on day 2 post-vaccine) (table 3) (Belshe *et al.* 1998, 2000*a*). After revaccination no significant differences in rhinorrhoea, fever or decreased activity were present (Belshe *et al.* 2000*a*). Live vaccine induced significantly more frequent haemagglutination inhibition (HAI) responses and higher titred responses to a range of H3N2 viruses including A/Sydney/5/97 (H3N2), Thessalonika/1/95 (H3N2), Russia/13919/95 (H3N2), and Johannesburg/33/94 (H3N2) in young children compared with the inactivated vaccine (figure 1) (Gruber *et al.* 1998; Belshe & Gruber 2000). Although significant differences in age between children in the live vaccine and inactivated vaccine groups may account for this more broad immune response, live vaccine will induce antibodies in children as young as 2 months of age (Belshe *et al.* 1992; Swierkosz *et al.* 1994).

CAIV-T was highly efficacious at preventing culture-confirmed influenza (table 4); in year 1 vaccine had 95% efficacy versus H3N2 (Wuhan- or Nanchang-like viruses) and 91% efficacy versus B. In year 2 the epidemic consisted largely of a variant not contained in the vaccine, influenza A/Sydney. In year 2 the epidemic of A/Sydney/5/97-like viruses caused 66 out of 71 cases with the remaining cases associated with A/Wuhan/359/95-like viruses (four cases) or influenza B (one case). Vaccine was 100% efficacious in year 2 against strains included in the vaccine and 86% efficacious against the variant, A/Sydney/5/97. Overall during the 2 years of study, vaccine was 92% efficacious at preventing culture-confirmed influenza (Belshe *et al.* 2000*a*). Challenge studies with H1N1 vaccine strain confirmed high efficacy against this virus (Belshe *et al.* 2000*b*).

Influenza-associated otitis media was significantly reduced in each year of the study. In year 1, there was only one case of influenza-associated otitis media in the vaccinated group, but there were 20 cases of otitis media among the placebo recipients associated with culture-positive influenza (VE = 98%). In year 2, only two cases of otitis media were associated with influenza in the vaccinated group, but 17 occurred in the placebo recipients (VE = 94%). Cases of lower respiratory disease associated with culture-positive influenza were also

Table 1. Summary of virulent influenza challenge studies in adults after CAIV-T or TIV vaccine. Results of challenge with virulent H1N1, H3N2 and B viruses are combined.

(Data from Treanor *et al*. (1999).)

vaccine	number vaccinated and challenged	number with infection and illness (%)	efficacy (%)[a]
CAIV-T	29	2 (7)	85
TIV	32	4 (13)	71
placebo	31	14 (45)	–

[a] Efficacy of CAIV-T or TIV versus placebo, respectively.

Table 2. Effectiveness of CAIV-T in healthy, working adults (aged 18–49 years) during influenza A/Sydney outbreak of 1997–1998.

(Data from Nichol *et al*. (1999).)

outcome	reduction (%) (95% CI) in indicated outcome in vaccinated versus placebo recipients
number of severe febrile illnesses	19 (7–29)
number of days with febrile URI[a] (FURI)	24 (13–33)
days of missed work for FURI	28 (16–39)
days of antibiotic use for FURI	45 (35–54)

[a] URI, upper respiratory infection.

Table 3. Safety of CAIV-T in children: comparison of mild adverse events on post-vaccine day 2 after either dose 1 or dose 2 in year 1 or after revaccination in year 2 among children receiving CAIV-T or placebo.

(Data from Belshe *et al*. (1998, 2000*a*).)

	event (%) in group			
	runny nose or nasal congestion		fever[a]	
dose of vaccine or placebo	vaccine	placebo	vaccine	placebo
year 1 vaccine dose 1	27[b]	18[b]	6.5[c]	1.6[c]
year 1 vaccine dose 2[d]	23	21	1.1	0.8
year 2 revaccination	19	14	2.0	1.8

[a] Temperature $> 38.1\,^{\circ}$C rectal or aural or $> 37.6\,^{\circ}$C axillary.
[b] $p < 0.01$.
[c] $p < 0.01$; note the mean maximum temperature among vaccinated children with fever was $38.2\,^{\circ}$C and the mean duration was 1.4 days. If temperature $> 38.3\,^{\circ}$C was used as the cut-off, $p =$ n.s.
[d] $p =$ n.s. for other comparisons.

significantly reduced in the vaccinated group; only one case occurred in the 2 years in the vaccinated group, but there were 11 cases in the 2 years in the placebo recipients (VE = 95% against influenza culture-positive lower respiratory disease).

Several measures of vaccine effectiveness were assessed as indicators of benefit from annual vaccination (table 5). Significant reduction in all febrile illness (regardless of result of viral cultures), reduction in febrile otitis media and reduction in associated antibiotic use was apparent in the vaccinated groups (Belshe & Gruber 2000). Similarly, reduction in lost day care or lost school days and reduction in lost work days by parents were present in the vaccinated children. Vaccinated children also visited health-care workers significantly less often.

6. DISCUSSION

CAIV-T provided high efficacy against influenza and effectiveness against influenza-associated illnesses in children and adults. Adult and children's studies included a year (1997–1998) in which the influenza strains selected for inclusion in the vaccine did not closely match the circulating predominant strain, influenza A/Sydney/5/97. The high efficacy against a variant influenza strain suggests that the live attenuated vaccine may provide superior immunity compared to inactivated vaccine in years when there is a poor match between vaccine and circulating viruses. The 2 years of study in children allowed us to estimate the efficacy of natural infection in year 1 against repeat infection in year 2. Of 53 placebo

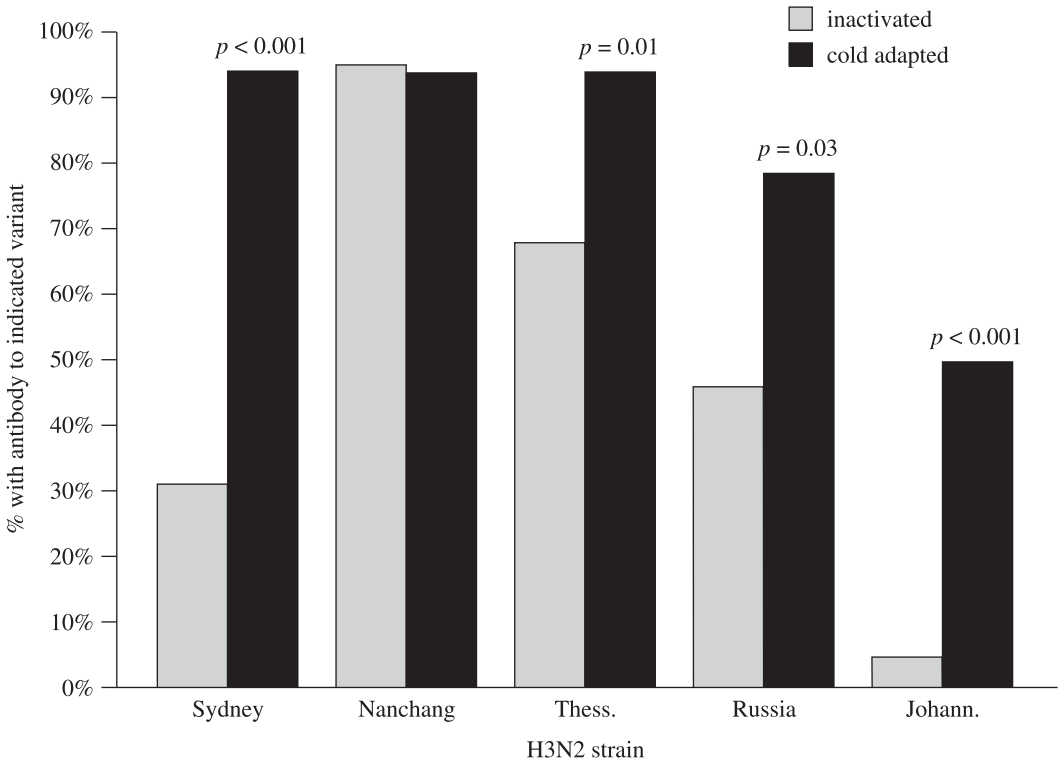

Figure 1. Percentage of children given two doses of CAIV-T (dark bars) or two doses of TIV (light bars) with HAI antibody post-vaccine to the indicated variant of H3N2. *p*-values indicate significant differences. Vaccines contained A/Nanchang/933/95 (H3N2) antigen (inactivated vaccine) or Nanchang-like antigen (live vaccine contained A/Wuhan/359/95-like H3N2). Thess. refers to A/Thessalonika/1/95 (H3N2); Russia refers to A/Russia/13919/95 (H3N2); and Johann. refers to A/Johannesburg/33/94 (H3N2). Reproduced with permission from *Pediatric Infectious Diseases Journal*, Lippincott Williams & Wilkins, Inc., Philadelphia, PA, USA.

Table 4. Protection against infection by CAIV-T in children. Occurrence of culture-positive influenza among study children in 1996–1997 (year 1) and 1997–1998 (year 2). Children in the vaccine group received CAIV-T in each year of this study.

(Data from Belshe *et al.* (1998, 2000*a*).)

	year 1		year 2	
	vaccine [a]	placebo	vaccine	placebo
number of children	1070	532	917	41
influenza A	7	63	15	55
influenza B	7	37	0	1
either	14	94[b]	15	56

[a] Overall VE was 92% (95% CI = 88–94) during the 2 years of study. In year 1 VE was 95% (95% CI = 88–97) versus influenza A and 91% (95% CI = 79–96) versus influenza B. In year 2 vaccine was 86% effective versus influenza A/Sydney (95% CI = 75–92).
[b] Six children had two illnesses, one A and one B.

children with culture-positive H3N2 in year 1, only one (1.9%) had H3N2 in year 2, but of 393 placebo children without culture-positive H3N2 in year 1, 54 (14%) had H3N2 infection and shedding in year 2. When these data are used to estimate the protective efficacy of natural infection with A/Wuhan (year 1) against A/Sydney (year 2), the result is 85% (95% confidence interval (CI) = 27–98). Point estimate of VE for the live attenuated vaccine (86%) was nearly identical to the point estimate of protection afforded by previous natural infection with A/Wuhan/369/95-like virus (85% efficacy) (Belshe *et al.* 2000*a*).

By what mechanism does the vaccine work? The induction of secretory IgA antibodies in the upper respiratory tract or the development of serum antibodies has been correlated with protection (Belshe *et al.* 2000*b*). Seropositive children infrequently develop serum antibodies in response to the live vaccine, and yet these children were also highly protected with the live attenuated vaccine (Belshe *et al.* 1998). VE was determined by age from less than 2 to more than 5 years: the results were 1 year old VE = 86%; 2 years old VE = 96%; 3 years old VE = 88%; 4 years old VE = 100%; 5 years old

Table 5. Effectiveness of CAIV-T in children in 1996–1997 (year 1) and 1997–1998 (year 2).

(Data from Belshe & Gruber (2000).)

	reduction (%) (vaccine versus placebo)	
effectiveness measure	year 1	year 2
febrile illness	21**	19**
OM[a]	9	8
febrile OM	33**	16
febrile illness with Abx[b]	29**	13
febrile OM with Abx	33**	18
days of missed day care	11	18**
days of parent missing work	18	6
visits to doctor	13**	8

[a] OM, otitis media.
[b] Abx, antibiotic.
**Statistically significant reductions in effectiveness parameter in the vaccinated group as compared with the placebo group.

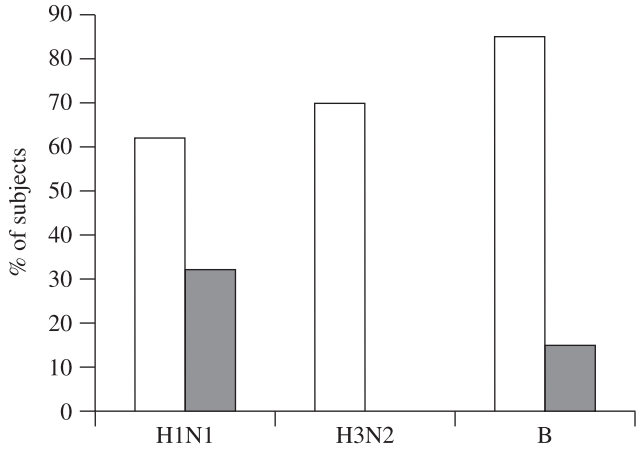

Figure 2. Per cent of children studied at Vanderbilt University with secretory IgA response to the indicated virus after two doses of CAIV-T (open bars, $n=13$) or placebo (hashed bars, $n=6$). Data from Boyce *et al*. 2000.

VE = 90%. Pre-existing antibody prevalence increased significantly among this range of ages and older children were more likely to have pre-existing antibody and no serum antibody response to live vaccine (Belshe *et al*. 1998). However, the efficacy results indicate that the fact that serum antibody is not boosted in seropositive individuals should not discourage use of the vaccine to prevent influenza. The development of secretory IgA is an important addition to immunity against influenza (figure 2). Other mediators of protection, including cell-mediated immunity, may also be induced by live attenuated vaccine. The safety, ease of administration of the vaccine, high efficacy, and high effectiveness make CAIV-T suitable for use in adults and children annually to prevent influenza and its complications.

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