Jornadas de Vacunas 2014 de la AEP

Nuevas vacunas antigripales

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ZARAGOZA 28 Y 29 DE MARZO

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Vacunas antigripales trivalentes inactivadas disponibles para uso en niños

- Vacunas de virus fraccionados
- Vacunas de subunidades
- Vacunas de subunidades virosómicas (adyuvadas)

Main critical issues and current desiderata for influenza vaccines

Critical issues	Desiderata
Suboptimal immunogenicity and protective efficacy in some target groups: - elderly subjects - patients with underlying chronic disease and immunocompromized - infants and young children	• Counter age-dependent immune decline • Elicit effective boosting • Create immunological memory • Improve priming and carry over
Mismatching between vaccinal and circulating strains (antigenic drift) **Annual re-licensure**	• Ensure cross-protection • Use of conserved viral antigen epitopes
Manufacture in embryonated eggs: - duration of the production process (nearly 6 months) - difficulties in the growth of the seed strains - delayed availability in the event of a pandemic - limited production capacity dependent upon availability of embryonated eggs - risk of vaccine shortage - increasing demand for vaccines worldwide	• Develope of alternative substrates and/or new technologies easy, rapid and high vaccine production • Allow antigen sparing

Durando P et al. Human Vaccines 7: Suppl 29-40; January/February 2011

Vacunas actualmente autorizadas en España

NOMBRE COMERCIAL	TIPO DE ANTIGENO	VIRUS CRECIDO EN	EXCIPIENTE-ADYUVANTE	RUTA DE ADMINISTRACIÓN	CANTIDAD DE HA DE CADA CEPA (MCG)	INDICADA PARA (EDAD)
Certat	Antígenos de superficie	Huevos embrionados	-	Intramuscular	15	>6 meses
Chiroflu	Antígenos de superficie	Huevos embrionados	-	Intramuscular	15	>6 meses
Chiromas	Antígenos de superficie	Huevos embrionados	Adyuvante MF59C.1	Intramuscular	15	≥ 65 años
Dotaricin	Antígenos de superficie	Huevos embrionados	Adyuvante MF59C.1	Intramuscular	15	≥ 65 años
Fluarix	Virus fraccionados	Huevos embrionados	-	Intramuscular	15	>6 meses
Fluenz	Vírus vivos atenuados	Huevos embrionados		Intranasal	15	≥ 24 meses a < 18 años
Gripavac	Virus fraccionados	Huevos embrionados	-	Intramuscular	15	>6 meses
Influvac	Antígenos de superficie	Huevos embrionados	-	Intramuscular	15	>6 meses
Inflexal V	Antígenos de superficie	Huevos embrionados	Virosomas	Intramuscular	15	>6 meses
Intanza 9 microgramos	Virus fraccionados	Huevos embrionados	-	Intradérmica	9	18-59 años
Intanza 15 microgramos	Virus fraccionados	Huevos embrionados	-	Intradérmica	15	≥ 60 años
Mutagrip	Virus fraccionados	Huevos embrionados	-	Intramuscular	15	>6 meses
Optaflu	Antígenos de superficie	Cultivo de tejido (células MDCK)	-	Intramuscular	15	≥ 18 años
Preflucel	Virus fraccionados	Cultivo de tejidos (células VERO)	-	Intramuscular	15	≥ 18 años
Vacuna antigripal Pasteur	Virus fraccionados	Huevos embrionados	-	Intramuscular	15	>6 meses

Nuevas vacunas de la gripe

- Adyuvadas
- Tetravalentes
- Intradérmicas
- Preparadas en cultivos celulares
- Basadas en genética inversa
- Basadas en ADN
- Vacunas atenuadas

Inspection of a syringe containing influenza vaccine during filling process. The white color is due to the addition of the adjuvant MF59

Adjuvants used and others under investigation in the context of influenza vaccines

Adjuvant category	Types
Oil-in-water emulsions	• MF59* • AS03* • AF03** • CoVaccine HT**
Saponins and glycolipids	• QS-21*** • ISCOMATRIX** • Alpha-GalCer (alpha-galactosylceramide)**
Liposomes	• Virosomes* • CCS (ceramide carbamoyl-spermine)** • CAF01 (cationic liposomes and synthetic mycobacterial cord factor)** • Vaxfectin**

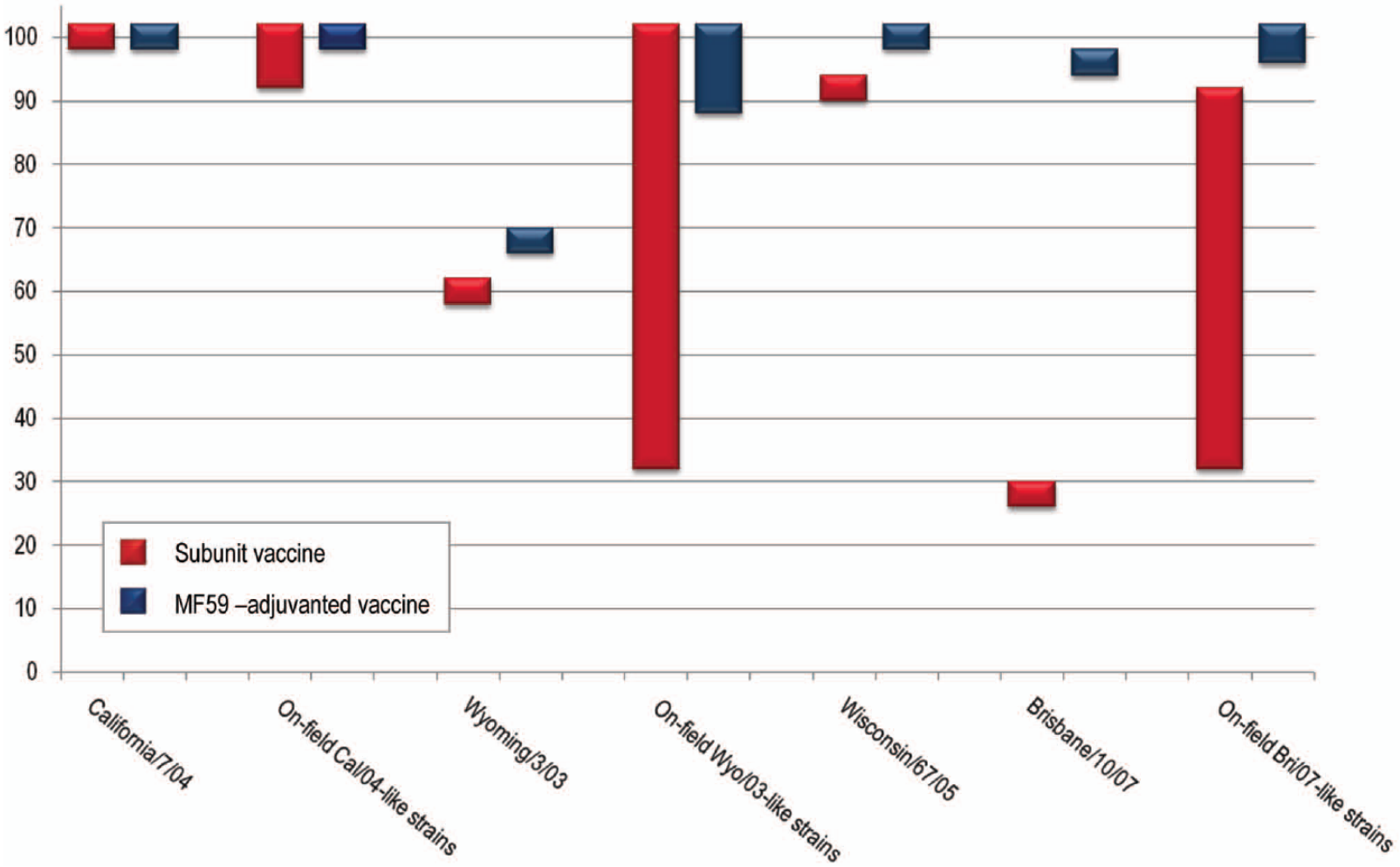
*in clinical use; **investigated in animal model; ***in clinical development

Durando P et al. Human Vaccines 2011; 7: Suppl 29-40

Adjuvant category	Types
Bacterial toxins/ components	• CT (Cholera toxin)**
	• LT (*Escherichia coli* labile enterotoxin)***
	• Chitosan**
	• Salmonella and *Escherichia coli* flagellins**
Cytokines	• IL-12, IL-23, IL-28B**
	• GM-CSF (Granulocyte-Macrophage Colony Stimulating Factor)**
	• Type 1 IFN (IFNalpha)**
TLR agonists/ immunomodulators	• Synthetic lipid A adjuvant (TLR-4)**
	• Bacterial flagellines (TLR-5)**
	• CpG (oligodeoxynucleotide) (TLR-9)***
	• Polyl:polyC12U [(synthetic double-stranded RNA (dsRNA)] (TLR-3)**
	• IC31 (oligodeoxynucleotide) (TLR-9)**
	• sLAG-3 (IMP321) (ligand for MHC class II)***

Durando P et al. Human Vaccines 2011; 7: Suppl 29-40

Comparison of the seroprotection rate (%) ranges, determined by HI assay, against the vaccine strain A/California/7/04, following vaccination with a MF59-adjuvanted vaccine and non-adjuvanted vaccine, according to several viral strains different from that included in the vaccine



Durando P et al. Human Vaccines 2011; 7: Suppl 29-40

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Oil-in-Water Emulsion Adjuvant with Influenza Vaccine in Young Children

Timo Vesikari, M.D., Markus Knuf, M.D., Peter Wutzler, M.D., Aino Karvonen, M.D., Dorothee Kieninger-Baum, M.D., Heinz-Josef Schmitt, M.D., Frank Baehner, M.D., Astrid Borkowski, M.D., Theodore F. Tsai, M.D., and Ralf Clemens, M.D.

N Engl J Med 2011;365:1406-16

OCTOBER 13, 2011

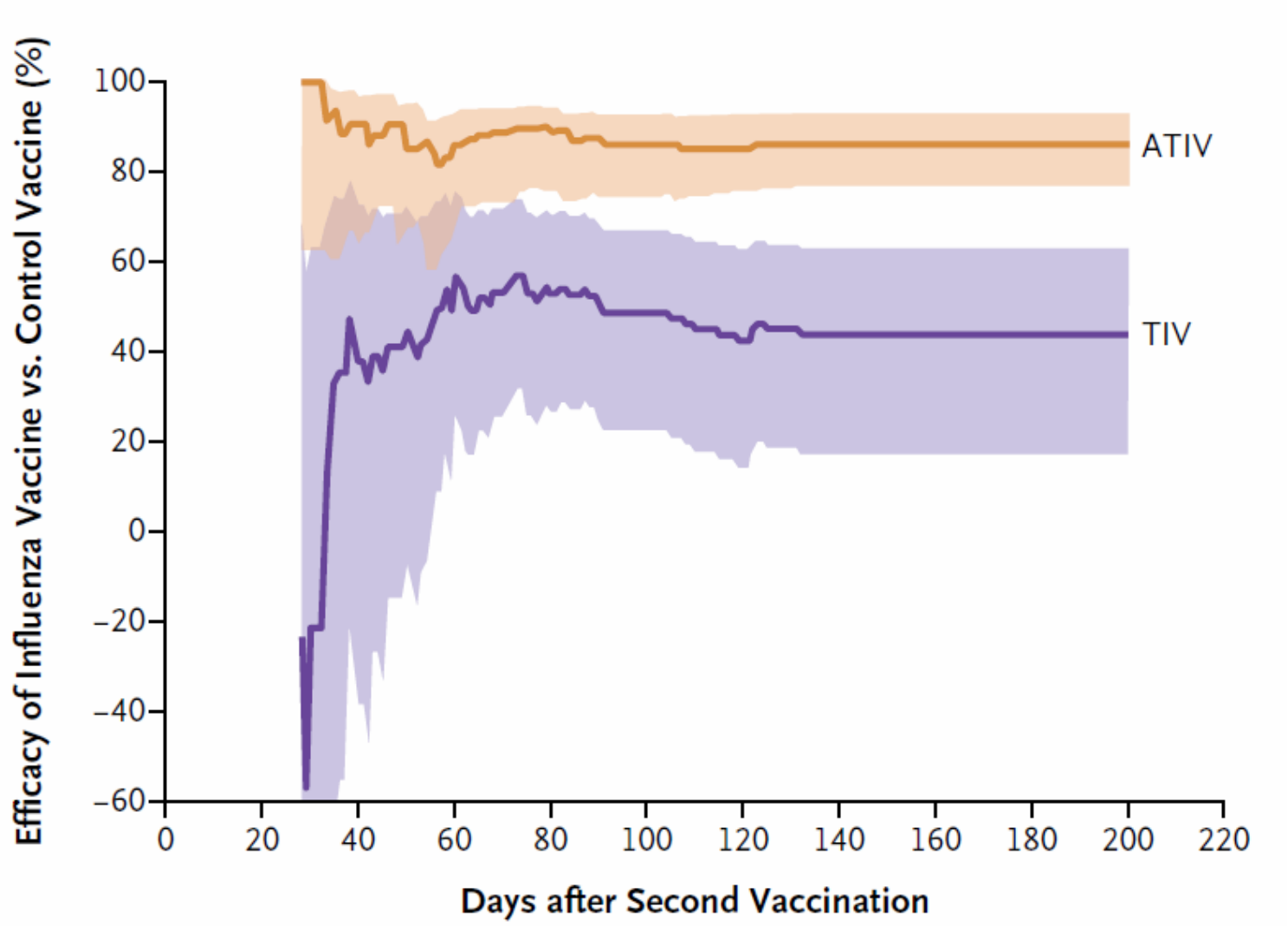
Efficacy of MF59-adjuvant trivalent influenza vaccine (ATIV), trivalent influenza vaccine without adjuvant (TIV), and control (noninfluenza) vaccine against confirmed influenza over two seasons (2007–2008 and 2008–2009) in Finland and Germany

Vesikari T et al. N Engl J Med 2011;365:1406-16

Age Group and Vaccine	Confirmed Cases of Influenza	Relative Efficacy (95% CI)†
	no. of children/total no.	*percent*
Efficacy against vaccine-matched strains		
6 to <72 mo		
ATIV vs. control	9/1937 vs. 41/993	89 (78 to 95)
TIV vs. control	44/1772 vs. 41/993	45 (16 to 64)
ATIV vs. TIV	9/1937 vs. 44/1772	80 (59 to 90)
36 to <72 mo		
ATIV vs. control	2/834 vs. 22/427	96 (81 to 99)
TIV vs. control	22/777 vs. 22/427	48 (8 to 71)
ATIV vs. TIV	2/834 vs. 22/777	91 (63 to 98)
6 to <36 mo		
ATIV vs. control	7/1103 vs. 19/566	81 (49 to 93)
TIV vs. control	22/995 vs. 19/566	41 (−9 to 68)
ATIV vs. TIV‡	7/1103 vs. 22/995	68 (27 to 86)
6 to <24 mo		
ATIV vs. control‡	4/820 vs. 8/401	75 (20 to 92)
TIV vs. control‡	15/706 vs. 8/401	2 (−129 to 58)
ATIV vs. TIV‡	4/820 vs. 15/706	75 (25 to 91)

Vesikari T et al. N Engl J Med 2011;365:1406-16

Efficacy of influenza vaccines versus control vaccine over time



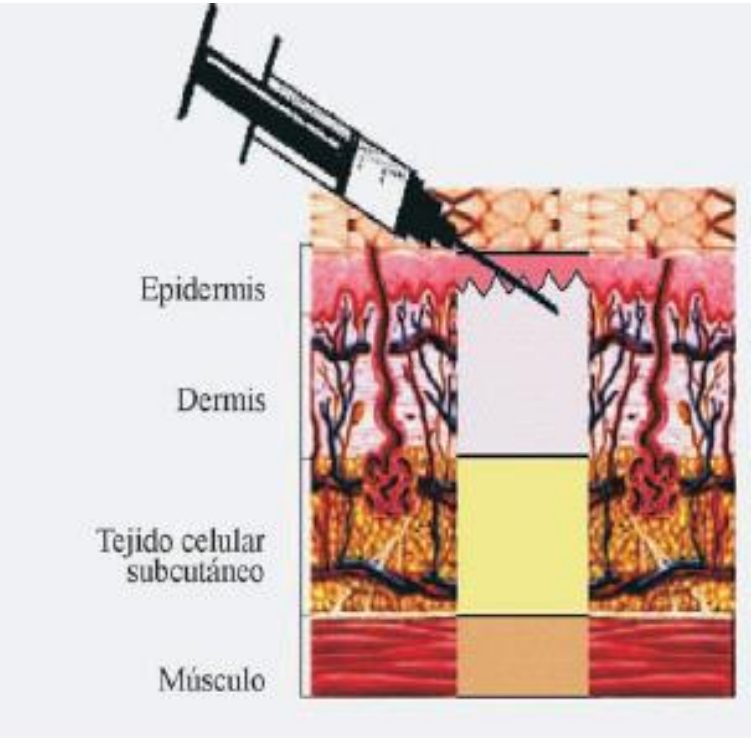
The cumulative efficacy of ATIV and of TIV, as compared with control (noninfluenza) vaccine, is shown. The data are for efficacy against all viral strains over time after the second dose of vaccine in children 6 to less than 72 months of age. Shaded areas represent 95% confidence intervals.

Vesikari T et al. N Engl J Med 2011;365:1406-16

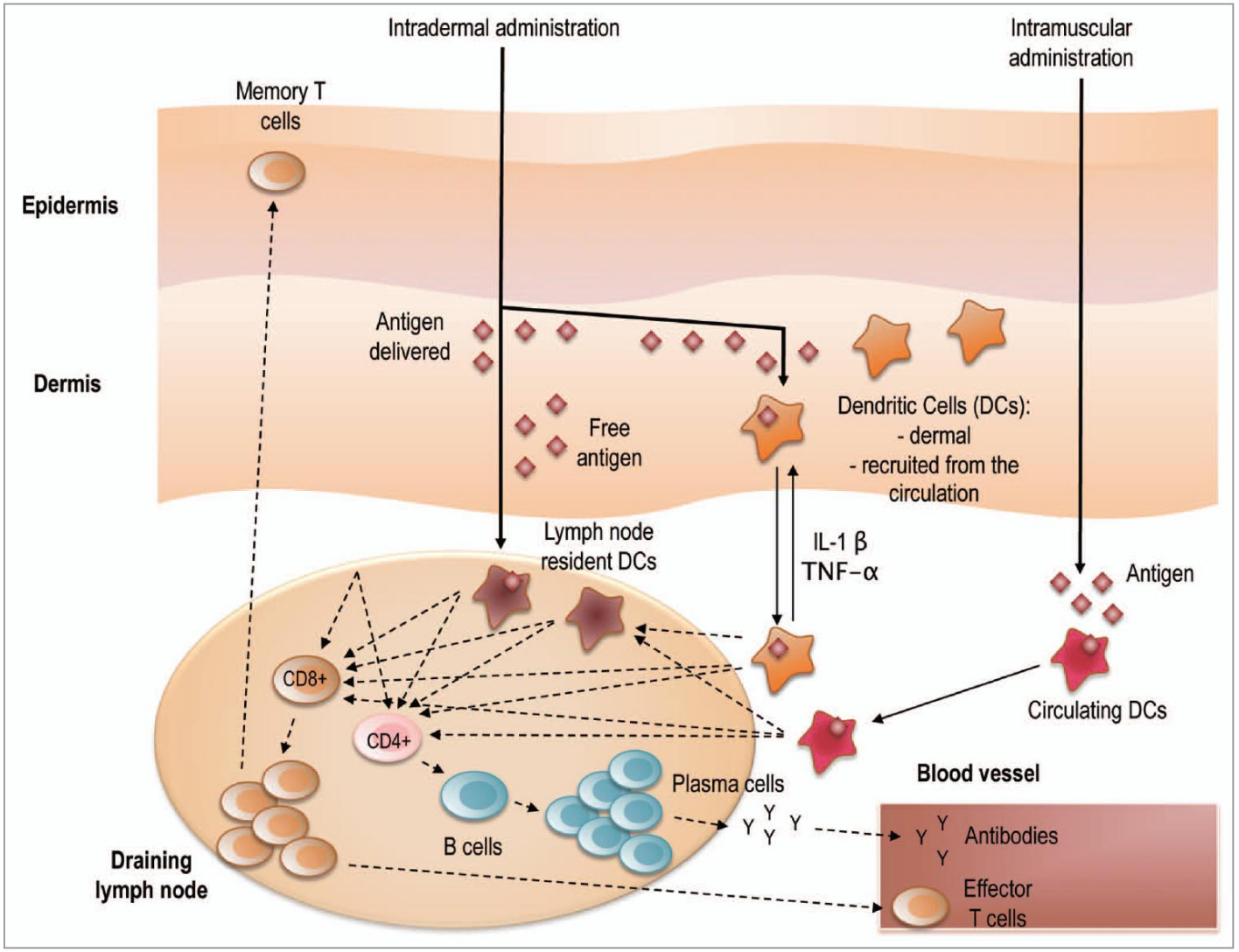
“The use of TIV with the MF59 adjuvant, which we studied, is a potentially effective option for children 6 to less than 72 months of age, with the additional potential advantages of increased heterovariant coverage, a longer duration of protection, and, for some strains, protection after a single dose.”

Vesikari T et al. N Engl J Med 2011;365:1406-16

Vacunas antigripales intradérmicas



Mechanisms and cells involved in the innate and adaptive immune response following administration of a vaccine antigen using the **intradermal** and intramuscular route

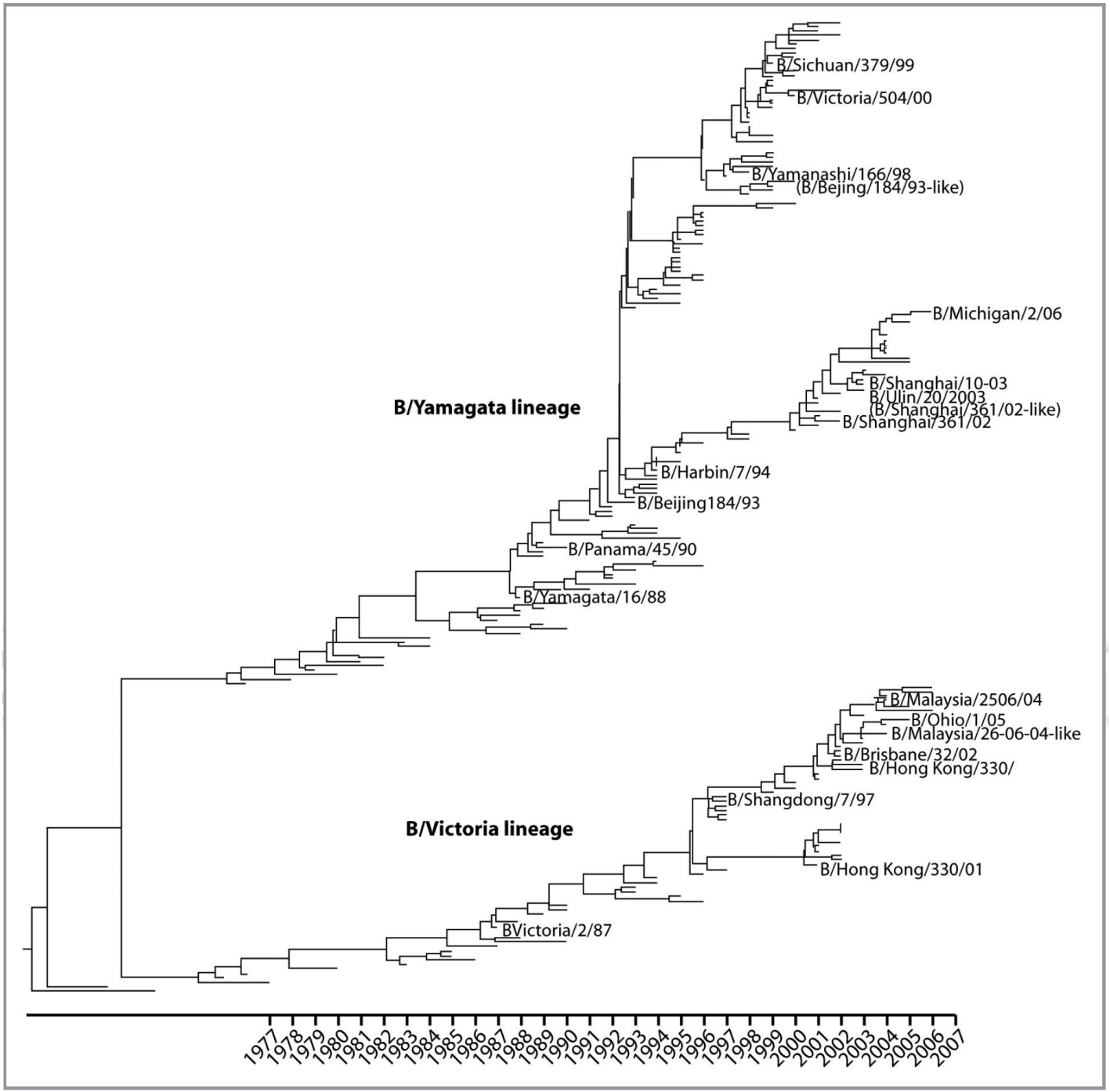


Durando P et al. Human Vaccines 7: Suppl 29-40; January/February 2011

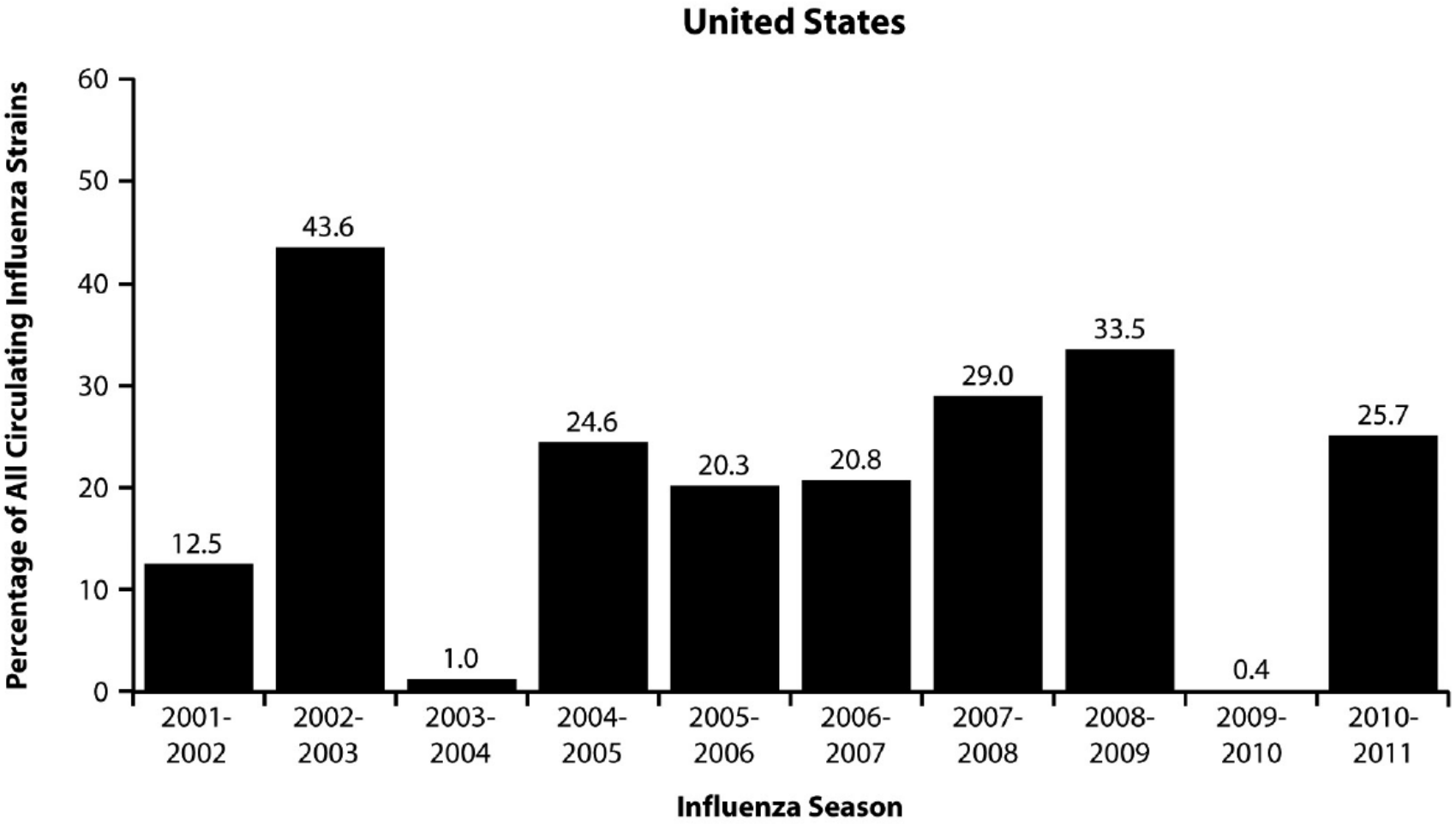
Vacunas antigripales de cultivos celulares y de ADN

Vacunas antigripales inactivadas tetravalentes

Evolution of two antigenically distinct lineages of influenza B (1970–2006)

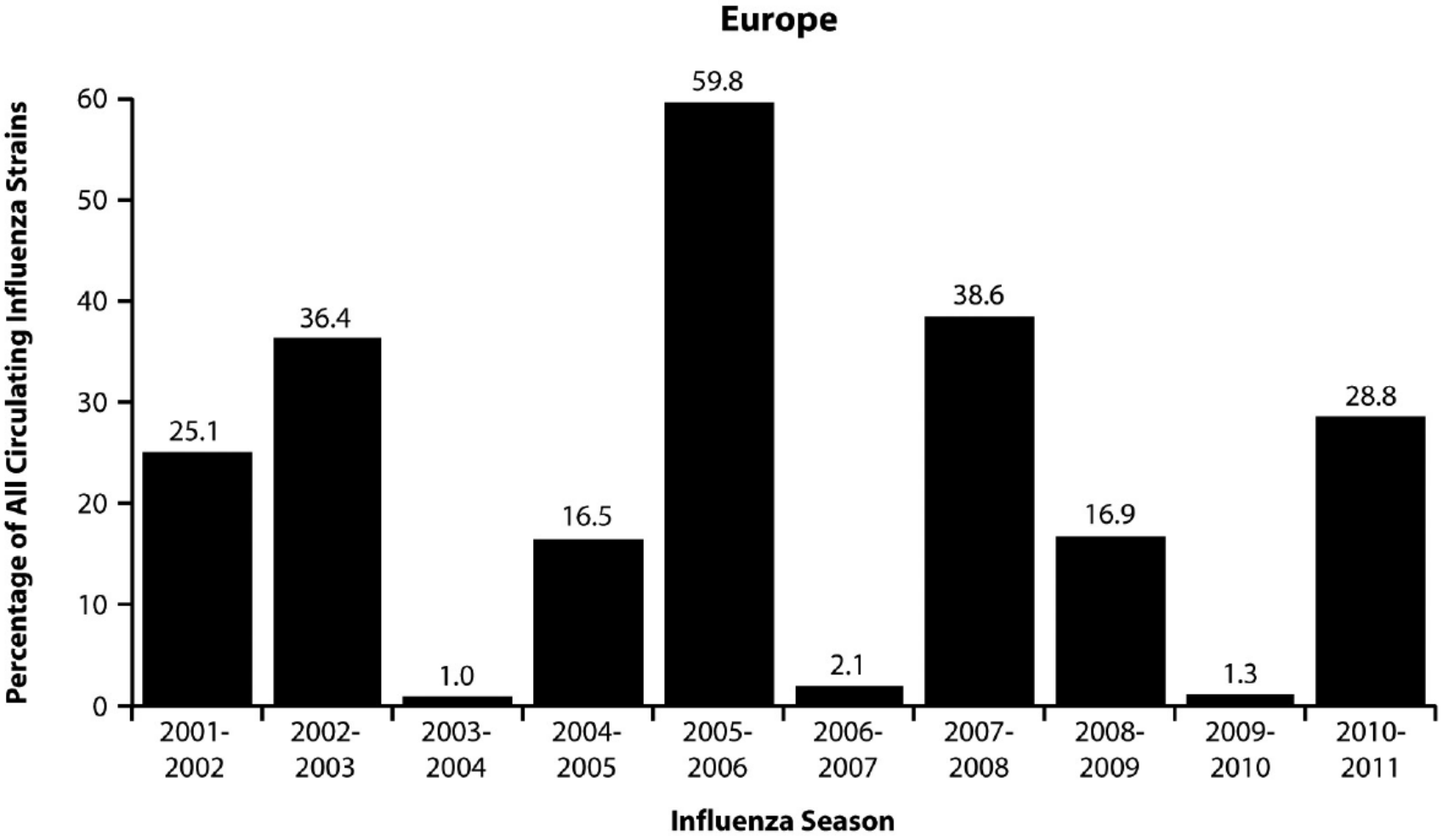


Influenza B circulation as a proportion of circulating influenza strains: US data for 2001 to 2011



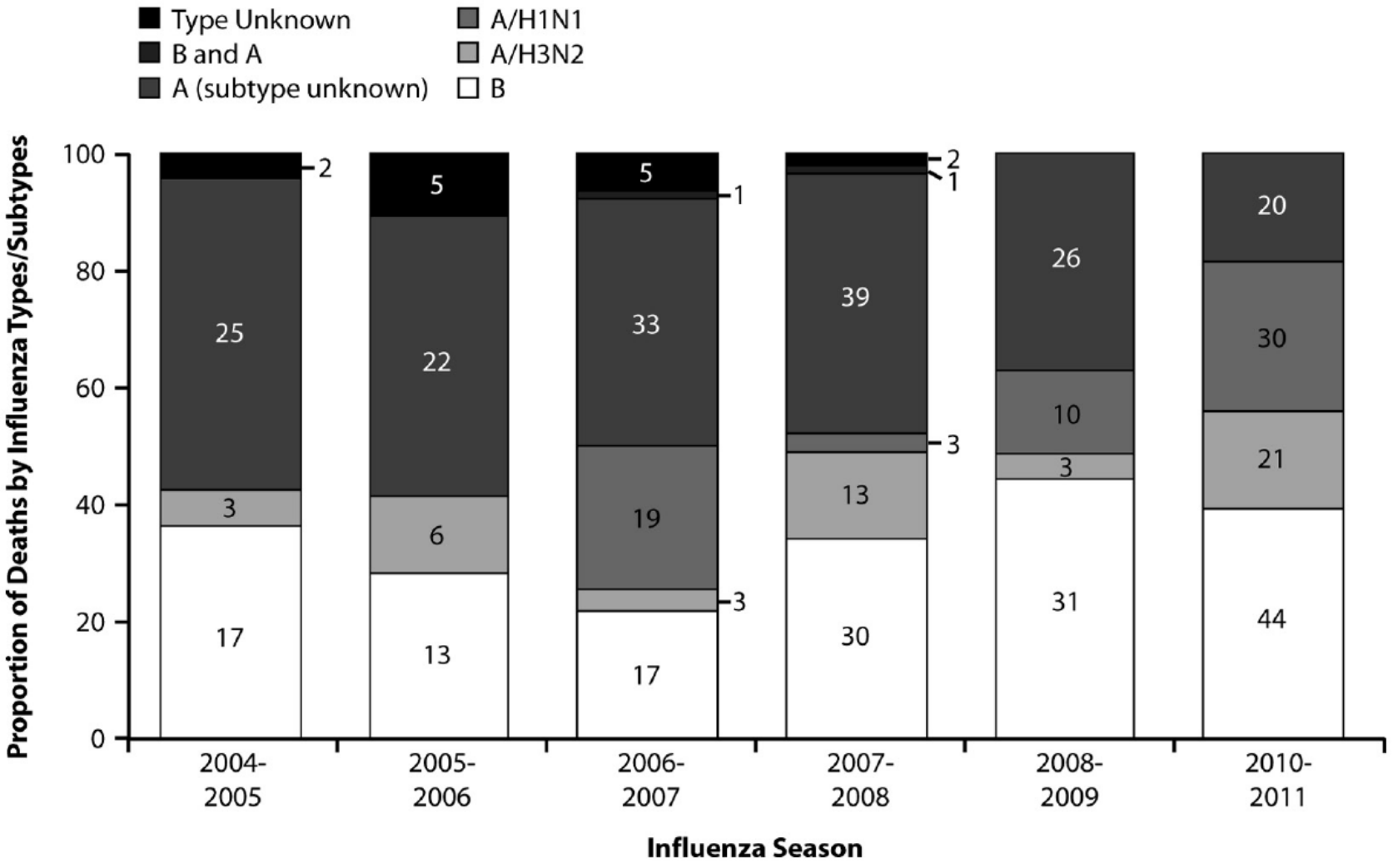
Ambrose CS et al. Human Vaccines & Immunotherapeutics 8:1, 81–88; January 2012

Influenza B circulation as a proportion of circulating influenza strains: European data for 2001 to 2011



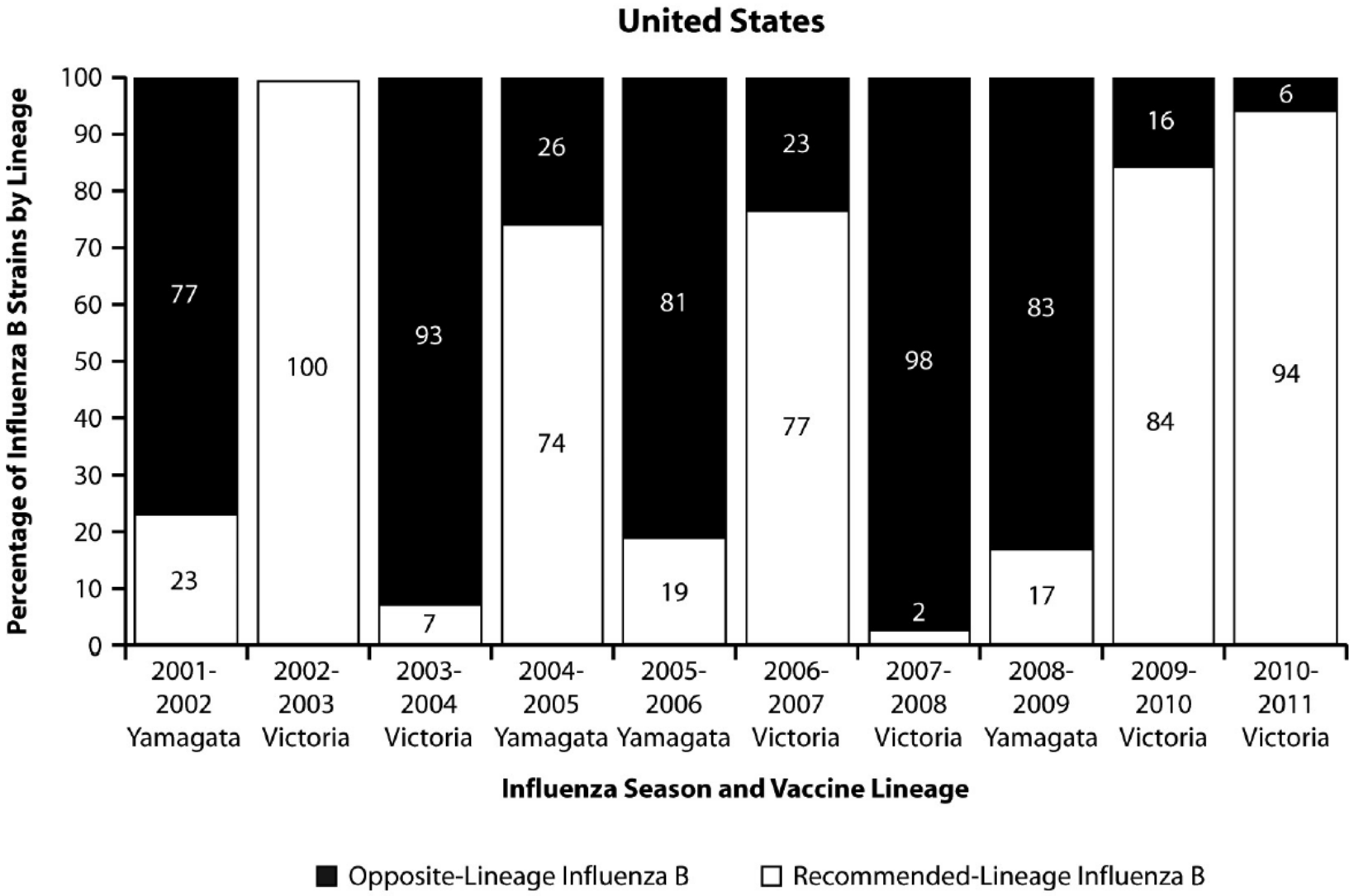
Ambrose CS et al. Human Vaccines & Immunotherapeutics 8:1, 81–88; January 2012

Proportion of US pediatric influenza deaths by viral type (2004 to 2011, excluding 2009–2010 pandemic). Values in columns represent the number of deaths in each category for each season



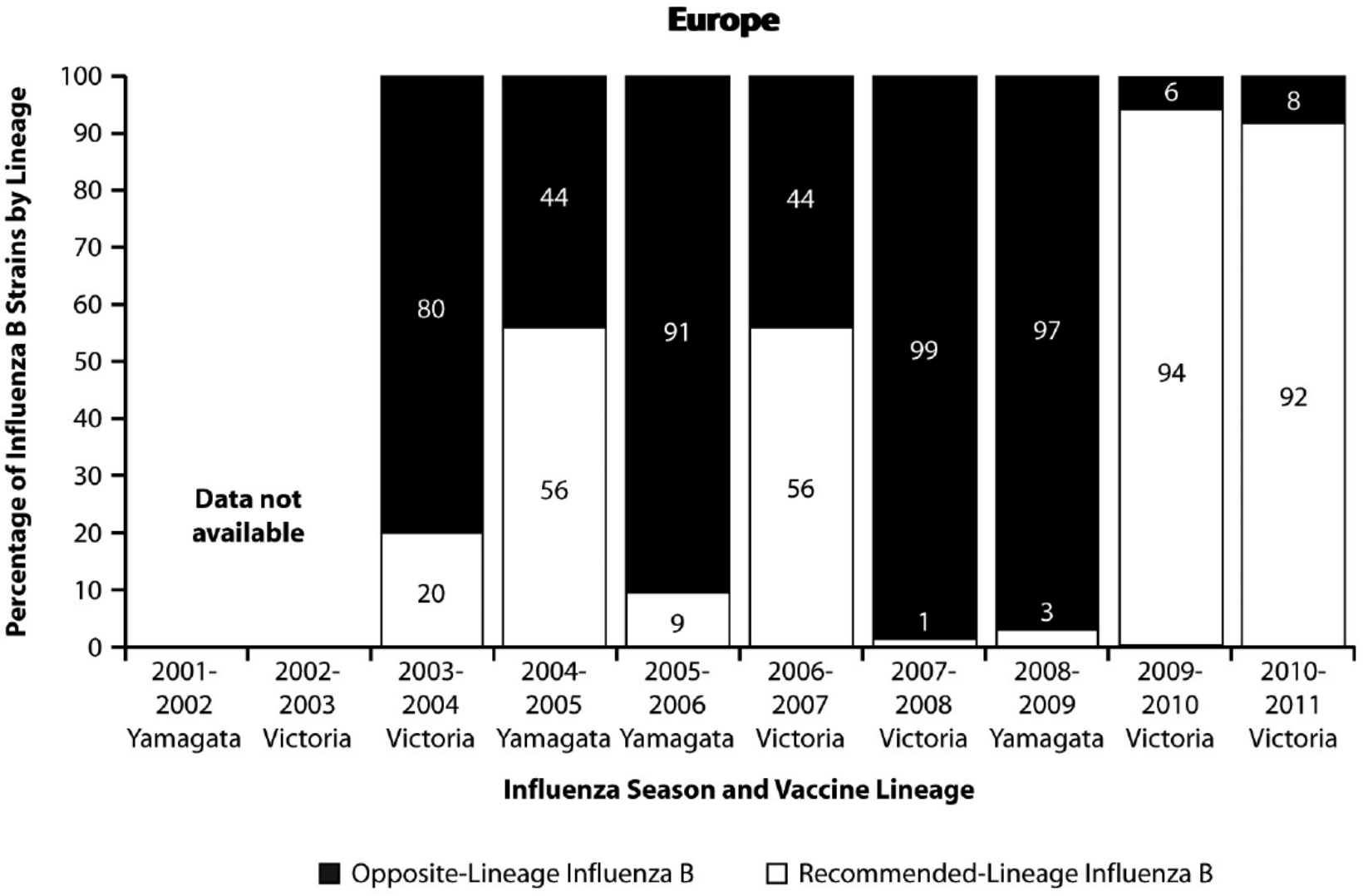
Ambrose CS et al. Human Vaccines & Immunotherapeutics 8:1, 81–88; January 2012

Influenza B circulation by lineage: US data for 2001 to 2011



Ambrose CS et al. Human Vaccines & Immunotherapeutics 8:1, 81–88; January 2012

Influenza B circulation by lineage: European data for 2001 to 2011



Ambrose CS et al. Human Vaccines & Immunotherapeutics 8:1, 81–88; January 2012

Nuevas vacunas atenuadas de la gripe

- virus vivos atenuados adaptados al frío
- administración intranasal
- trivalentes y tetravalentes

Live Attenuated Influenza Vaccine (FluMist®; Fluenz™)

A Review of its Use in the Prevention of Seasonal Influenza in Children and Adults

Natalie J. Carter and *Monique P. Curran*

Drugs 2011; 71 (12): 1591-1622

Live attenuated influenza vaccine (LAIV) is an intranasally administered trivalent, seasonal influenza vaccine that contains three live influenza viruses (two type A [H1N1 and H3N2 subtypes] and one type B).

LAIV was effective in protecting against culture-confirmed influenza caused by antigenically matched and/or distinct viral strains in children aged ≤71 months enrolled in three phase III trials. LAIV was superior to trivalent inactivated influenza vaccine (TIV) in protecting against influenza caused by antigenically-matching viral strains in a multinational phase III trial in children aged 6–59 months. LAIV was also significantly more effective than TIV in decreasing the incidence of culture-confirmed influenza illness in two open-label studies (in children with recurrent respiratory tract illnesses aged 6–71 months and in children and adolescents with asthma aged 6–17 years).

In conclusion, intranasal LAIV seasonal influenza vaccine is effective and well tolerated in children, adolescents and adults. LAIV was more effective than TIV in children, although this advantage was not seen in adults. In the US, LAIV is indicated for the active immunization of healthy subjects aged 2–49 years against influenza disease caused by virus subtypes A and type B contained in the vaccine.

LAIV was generally well tolerated in most age groups, with the majority of adverse events being mild to moderate in severity, and runny nose/nasal congestion being the most common. In a large phase III trial, LAIV, compared with TIV, was associated with an increased incidence of medically significant wheezing in vaccine-naive children aged <24 months and an increased incidence of hospitalization in children aged 6–11 months; LAIV is not approved for use in children <24 months.

LAIV was not always associated with high rates of seroconversion/seroresponse, particularly in older children and adults, or in subjects with detectable levels of haemagglutination-inhibiting antibodies at baseline. However, LAIV did elicit mucosal (nasal) IgA antibody responses and strong cell-mediated immunity responses. Only one confirmed case of LAIV virus transmission to a placebo recipient (who did not become ill) occurred in a transmission study conducted in young children. The immunogenic response to LAIV in young healthy children was not affected by concomitant administration with other commonly administered childhood vaccines.

Drugs 2011; 71 (12): 1591-1622

The efficacy of intranasal live attenuated influenza vaccine in children 2 through 17 years of age: A meta-analysis of 8 randomized controlled studies

Christopher S. Ambrose[a,*], Xionghua Wu[b], Markus Knuf[c,d], Peter Wutzler[e]

Vaccine 30 (2012) 886–892

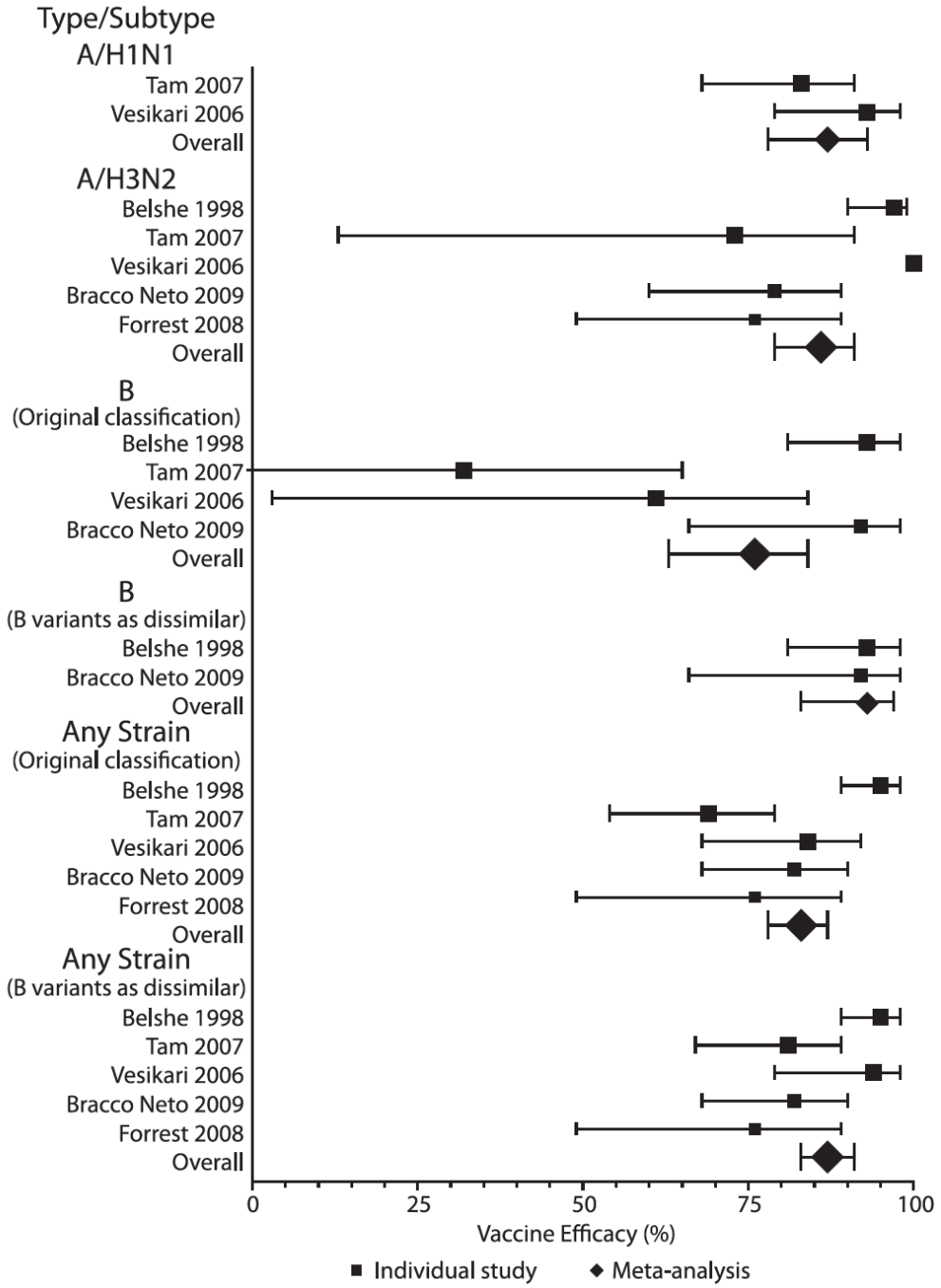
Background: Nine randomized controlled clinical trials, including approximately 26,000 children aged 6 months to 17 years, have evaluated the efficacy of live attenuated influenza vaccine (LAIV) against culture-confirmed influenza illness compared with placebo or trivalent inactivated influenza vaccine (TIV). The objective of the current analysis was to integrate available LAIV efficacy data in children aged 2–17 years, the group for whom LAIV is approved for use.

Methods: A meta-analysis was conducted using all available randomized controlled trials and a fixed-effects model. Cases caused by drifted influenza B were analyzed as originally classified and with all antigenic variants classified as dissimilar.

Results: Five placebo-controlled trials (4 were 2-season trials) and 3 single-season TIV-controlled trials were analyzed. Compared with placebo, year 1 efficacy of 2 doses of LAIV was 83% (95% CI: 78, 87) against antigenically similar strains; efficacy was 87% (95% CI: 78, 93), 86% (95% CI: 79, 91), and 76% (95% CI: 63, 84) for A/H1N1, A/H3N2, and B, respectively. Classifying B variants as dissimilar, efficacy against all similar strains was 87% (95% CI: 83, 91) and 93% (95% CI: 83, 97) against similar B strains. Year 2 efficacy was 87% (95% CI: 82, 91) against similar strains. Compared with TIV, LAIV recipients experienced 44% (95% CI: 28, 56) and 48% (95% CI: 38, 57) fewer cases of influenza illness caused by similar strains and all strains, respectively. LAIV efficacy estimates for children from Europe, the United States, and Middle East were robust and were similar to or higher than those for the overall population.

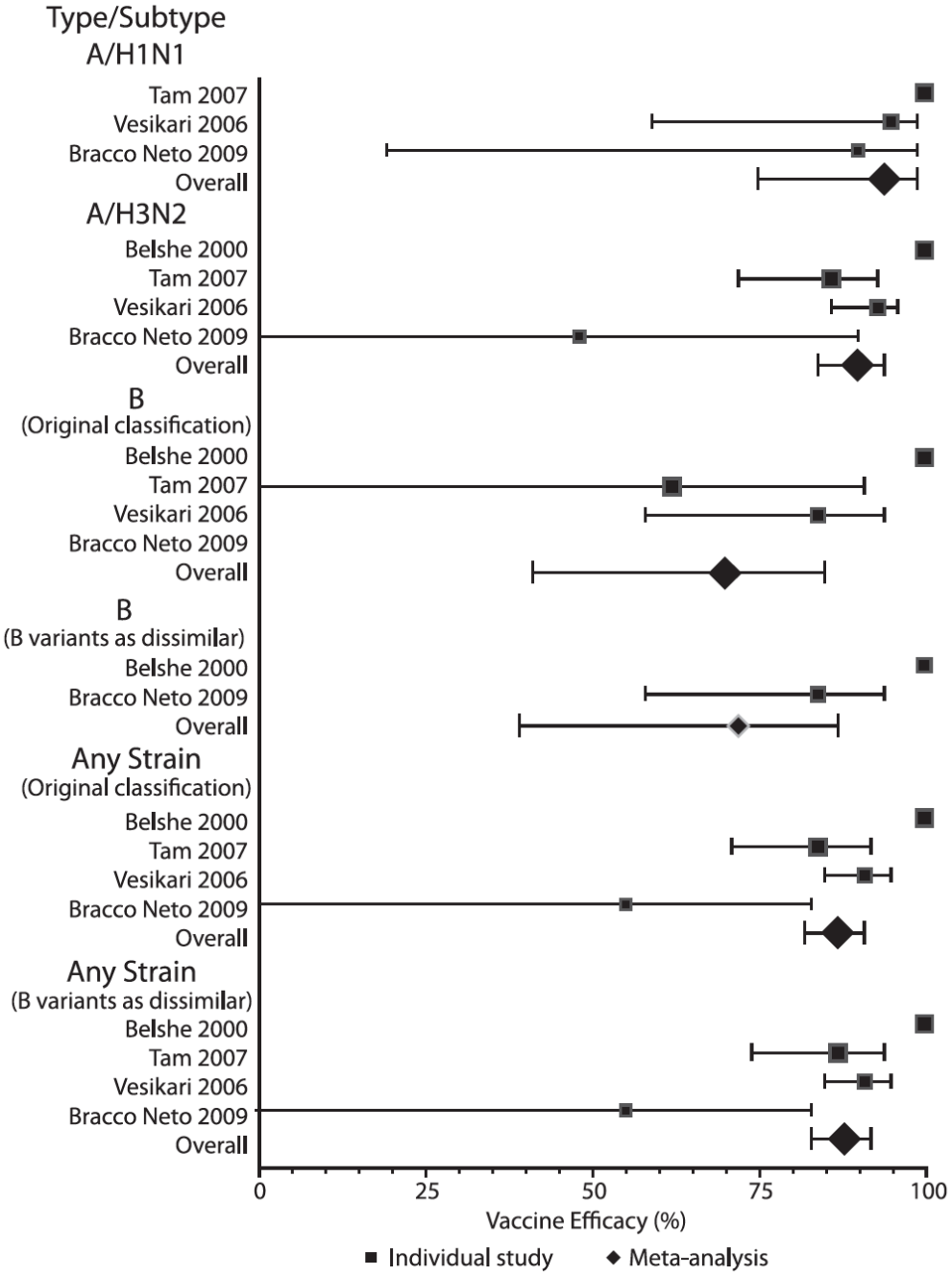
Conclusions: In children aged 2–17 years, LAIV demonstrated high efficacy after 2 doses in year 1 and revaccination in year 2, and greater efficacy compared with TIV. This meta-analysis provides precise estimates of LAIV efficacy among the approved pediatric age group.

Live attenuated influenza vaccine efficacy versus placebo (year 1; 2 doses) for antigenically similar strains by type/subtype and study



Symbol sizes are relative to the study population sizes

Live attenuated influenza vaccine efficacy versus placebo (year 2; 1 revacunation dose) for antigenically similar strains by type/subtype and study



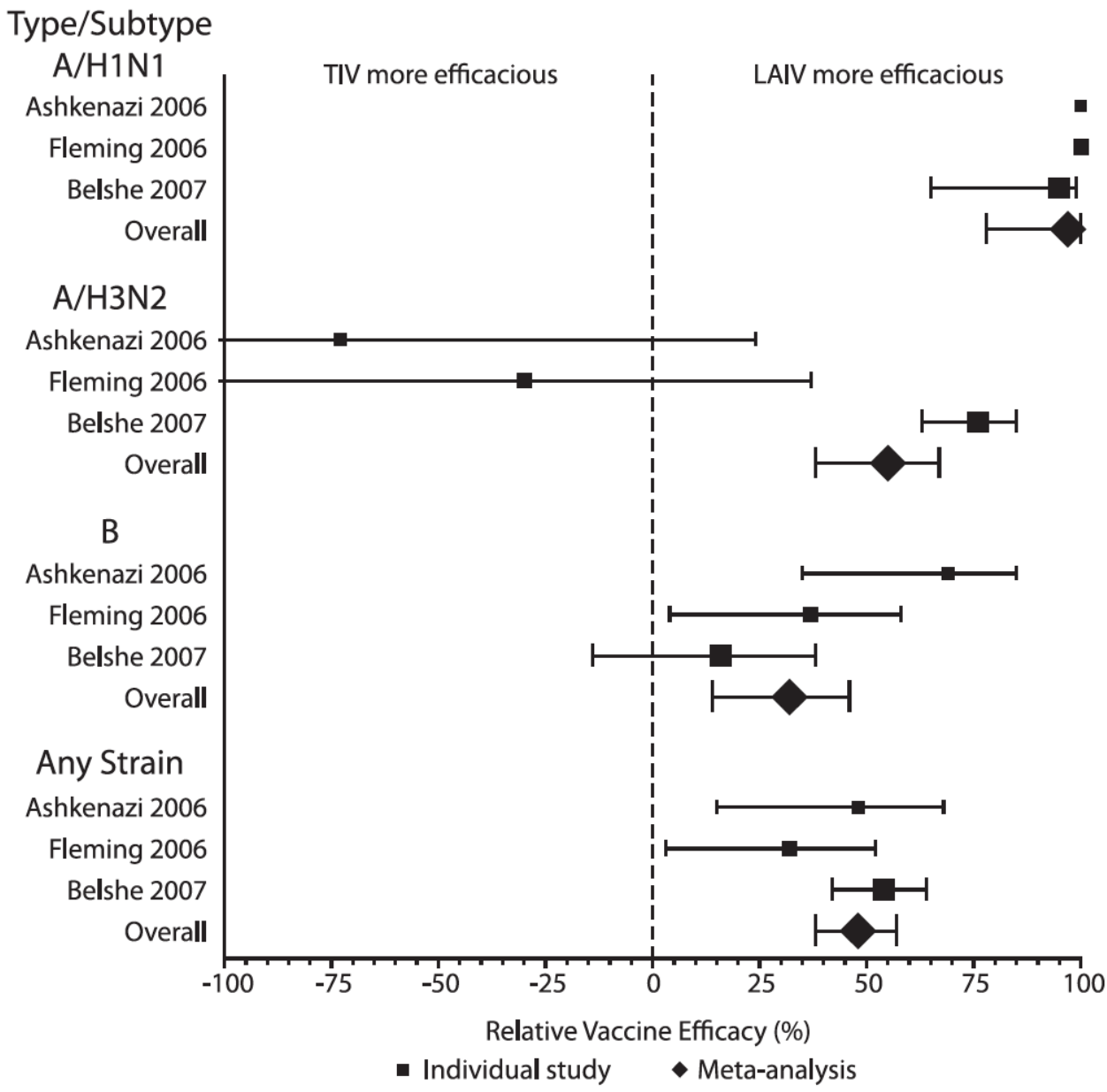
Symbol sizes are relative to the study population sizes

Efficacy of LAIV versus placebo in years 1 and 2

Influenza strain	LAIV *n*/*N* (%)	Placebo *n*/*N* (%)	Vaccine efficacy
Following year 1 vaccination, antigenically similar strains			
A/H1N1	14/1272 (1.1)	78/890 (8.8)	87 (78, 93)
A/H3N2	26/2542 (1.0)	135/1746 (7.7)	86 (79, 91)
B (original classification)	30/2333 (1.3)	82/1564 (5.2)	76 (63, 84)
B (variants as dissimilar)	6/1061 (0.6)	52/674 (7.7)	93 (83, 97)
Any strain (original classification)	70/2542 (2.8)	281/1746 (16.1)	83 (78, 87)
Any strain (B variants as dissimilar)	46/2542 (1.8)	260/1764 (14.5)	87 (83, 91)
Following year 1 vaccination, all strains regardless of antigenic similarity			
A/H1N1	14/1272 (1.1)	85/890 (9.6)	88 (80, 93)
A/H3N2	32/2542 (1.3)	143/1746 (8.2)	84 (77, 89)
B	47/2542 (1.8)	102/1746 (5.8)	68 (55, 77)
Any strain	94/2542 (3.7)	311/1746 (17.8)	79 (73, 83)
Following year 2 revaccination, antigenically similar strains			
A/H1N1	2/1606 (0.1)	27/1173 (2.3)	94 (75, 99)
A/H3N2	20/2354 (0.8)	137/1535 (8.9)	90 (84, 94)
B (original classification)	12/2354 (0.5)	28/1535 (1.8)	70 (41, 85)
B (variants as dissimilar)	9/1583 (0.6)	23/1041 (2.2)	72 (39, 87)
Any strain (original classification)	33/2354 (1.4)	183/1535 (11.9)	87 (82, 91)
Any strain (B variants as dissimilar)	30/2354 (1.3)	179/1535 (11.7)	88 (83, 92)
Following Year 2 Revaccination, All Strains Regardless of Antigenic Similarity			
A/H1N1	2/1606 (0.1)	27/1173 (2.3)	94 (75, 99)
A/H3N2	35/2354 (1.5)	186/1535 (12.1)	88 (84, 92)
B	55/2354 (2.3)	76/1535 (5.0)	43 (19, 59)
Any strain	91/2354 (3.9)	275/1535 (17.9)	78 (72, 82)

C.S. Ambrose et al. Vaccine 2012; 30:886-892

LAIV efficacy versus TIV (year 1; 2 doses) for all strains regardeless of antigenica similarity by type/subtype and study



LAIV: live attenuated influenza vaccine
TIV: trivalent inactivated influenza vaccine

Symbol sizes are relative to the study population sizes

C.S. Ambrose et al. Vaccine 2012; 30:886-892

Comparing influenza vaccine efficacy against mismatched and matched strains: a systematic review and meta-analysis

Andrea C Tricco[1], Ayman Chit[2,3], Charlene Soobiah[1], David Hallett[4], Genevieve Meier[6], Maggie H Chen[1], Mariam Tashkandi[5], Chris T Bauch[7] and Mark Loeb[8,9*]

BMC Medicine

BMC Medicine 2013, **11**:153

Abstract

Background: Influenza vaccines are most effective when the antigens in the vaccine match those of circulating strains. However, antigens contained in the vaccines do not always match circulating strains. In the present work we aimed to examine the vaccine efficacy (VE) afforded by influenza vaccines when they are not well matched to circulating strains.

Methods: We identified randomized clinical trials (RCTs) through MEDLINE, EMBASE, the Cochrane Library, and references of included RCTs. RCTs reporting laboratory-confirmed influenza among healthy participants vaccinated with antigens of matching and non-matching influenza strains were included. Two independent reviewers screened citations/full-text articles, abstracted data, and appraised risk of bias. Conflicts were resolved by discussion. A random effects meta-analysis was conducted. VE was calculated using the following formula: (1 - relative risk × 100%).

Results: We included 34 RCTs, providing data on 47 influenza seasons and 94,821 participants. The live-attenuated influenza vaccine (LAIV) showed significant protection against mismatched (six RCTs, VE 54%, 95% confidence interval (CI) 28% to 71%) and matched (seven RCTs, VE 83%, 95% CI 75% to 88%) influenza strains among children aged 6 to 36 months. Differences were observed between the point estimates for mismatched influenza A (five RCTs, VE 75%, 95% CI 41% to 90%) and mismatched influenza B (five RCTs, VE 42%, 95% CI 22% to 56%) estimates among children aged 6 to 36 months. The trivalent inactivated vaccine (TIV) also afforded significant protection against mismatched (nine RCTs, VE 52%, 95% CI 37% to 63%) and matched (eight RCTs, VE 65%, 95% CI 54% to 73%) influenza strains among adults. Numerical differences were observed between the point estimates for mismatched influenza A (five RCTs, VE 64%, 95% CI 23% to 82%) and mismatched influenza B (eight RCTs, VE 52%, 95% CI 19% to 72%) estimates among adults. Statistical heterogeneity was low (I^2 <50%) across all meta-analyses, except for the LAIV meta-analyses among children (I^2 = 79%).

Conclusions: The TIV and LAIV vaccines can provide cross protection against non-matching circulating strains. The point estimates for VE were different for matching versus non-matching strains, with overlapping CIs.

Live Attenuated Influenza Vaccine in Children Younger than 2 Years. A Systematic Review

*Gabriela J. Prutsky, MD, *†‡ Juan Pablo Domecq, MD,*‡§ Tarig Elraiyah, MB BS,* Larry J. Prokop, MLS,* and M. Hassan Murad, MD, MPH*¶*

Results: We found 7 eligible randomized controlled trials and 2 observational studies. Randomized controlled trials included 6281 children and were at low to moderate risk of bias. LAIV reduced the incidence of influenza compared with placebo (relative risk = 0.36, 95% confidence interval: 0.23–0.58, $P < 0.05$) with a number needed to vaccinate of 17. LAIV increased the incidence of minor side effects (fever and rhinorrhea). LAIV had a similar effect in preventing influenza (relative risk = 0.76, 95% confidence interval: 0.45–1.30, $P > 0.05$) compared with inactivated influenza vaccine. There was an increase of hospitalization rate (post hoc analysis) and medical attended wheezing with LAIV.

Conclusions: LAIV is highly effective in children <2 years of age compared with placebo and is as effective to inactivated influenza vaccine. The safety profile of LAIV is reasonable although evidence is sparse. LAIV may be considered as an option in this age group particularly during seasons with vaccine shortage.

Pediatr Infect Dis J 2014;33:e106–e115

New vaccines against influenza

Clin Exp Vaccine Res 2014;3:12-28

Young-Tae Lee et al • New influenza vaccine approaches

Vaccination is one of the most effective and cost-benefit interventions that prevent the mortality and reduce morbidity from infectious pathogens. However, the licensed influenza vaccine induces strain-specific immunity and must be updated annually based on predicted strains that will circulate in the upcoming season. Influenza virus still causes significant health problems worldwide due to the low vaccine efficacy from unexpected outbreaks of next epidemic strains or the emergence of pandemic viruses. Current influenza vaccines are based on immunity to the hemagglutinin antigen that is highly variable among different influenza viruses circulating in humans and animals. Several scientific advances have been endeavored to develop universal vaccines that will induce broad protection. Universal vaccines have been focused on regions of viral proteins that are highly conserved across different virus subtypes. The strategies of universal vaccines include the matrix 2 protein, the hemagglutinin HA2 stalk domain, and T cell-based multivalent antigens. Supplemented and/or adjuvanted vaccination in combination with universal target antigenic vaccines would have much promise. This review summarizes encouraging scientific advances in the field with a focus on novel vaccine designs.