Protection Against Influenza After Annually Repeated Vaccination

A Meta-analysis of Serologic and Field Studies

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Background: According to common recommendations, influenza vaccination should be performed annually. It has been suggested that vaccination in previous years reduces vaccine efficacy in the long term.

Objective: To determine whether the protection of influenza vaccine decreases when vaccination is repeated annually.

Methods: Articles published between 1966 and 1997 were selected from MEDLINE. The end point for field studies was the influenza-related morbidity or mortality during influenza outbreaks (resulting in field protection rates). The end point for serologic studies was exceeding a protective postvaccination hemagglutination-inhibition titer (serologic protection rates). Protection rate differences between groups with single and multiple vaccinations were subjected to meta-analysis.

Results: Seven field studies (including 13 trials) supported the hypothesis that protection in multiple-vaccination groups is at least as good as that in single-vaccination groups. Ten trials with 5117 observations could be subjected to meta-analysis. The pooled protection-rate difference was close to 0 (1.1%; 95% confidence interval, –0.2% to 2.4%), thus detecting no difference between single or multiple vaccination. Twelve serologic studies (including 53 trials) showed heterogeneous results: 9 trials were significantly in favor of single vaccination, and 7 were in favor of multiple vaccination, but in most cases, there was no significant difference between the 2 vaccination groups. The pooled serologic protection-rate difference from 52 trials (12 341 observations) was again close to 0 (1.7%; 95% confidence interval, –1.3% to 4.8%).

Conclusions: We did not detect any evidence for a decreasing protection with annually repeated influenza vaccination. Annual vaccination should not be discouraged in populations at risk.

Arch Intern Med. 1999;159:182-188

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VACCINATION strategies should result in effective protection. Current efforts with respect to influenza rightly focus on the prevention of pandemic influenza (pandemic planning),[1] but the effects on mortality and morbidity between pandemic periods should not be neglected. The number of deaths attributed to annual epidemic influenza during the past 60 years is many times greater than that attributed to pandemic influenza.[2] Recommendations for the use of inactivated influenza vaccine in humans proceed from the necessity to administer the vaccine every year[3] because the antigenic properties of wild influenza viruses change frequently, and antibody titer levels may decline to nonprotective levels within a year after vaccination. Hoskins et al[4] challenged this common policy by claiming that protection after annual influenza vaccination would successively decrease. Although doubts about the validity of the findings of Hoskins et al had been articulated,[5-8] uncertainty about the issue has remained, which may contribute to suboptimal vaccine use in people at risk.[9]

Evidence of influenza vaccine efficacy in humans is derived from 3 types of clinical studies: the experimental study, the field study, and the immune-response study (serologic study). In experimental studies, volunteers are challenged by live influenza viruses under strictly controlled circumstances. This approach is scientifically most satisfying but cannot be applied in populations at risk for serious complications from influenza infection. Field studies register morbidity or mortality during naturally occurring influenza outbreaks. Despite certain drawbacks and limitations of this approach,[10,11] field studies have convincingly proved the efficacy of single influenza vaccine.[7] Challenge studies in healthy children and young adults have es-

METHODS

SOURCES AND SELECTION OF LITERATURE

Titles and abstracts of articles published from January 1966 to December 1997 and included in the MEDLINE computerized library system (National Library of Medicine, Bethesda, Md) were checked for the combination of "influenza" and "vaccine" or "vaccination." The search strategy was limited to human studies (including articles in English, Dutch, German, French, Spanish, Italian, and Russian). A total of 2391 references were found to comply to this strategy. Next, all titles and abstracts were evaluated. Articles were selected for further reading if there was a reference to a study design comprising more than 1 year or if the words "revaccination," "annually repeated vaccination," "preimmunized," or "hemagglutination inhibition" (HI) were used. This selection produced 431 references. Also, cross-references in already identified articles were included. These articles were then read in search of information on the effect of annually repeated vaccination.

In the case of field studies, any article was accepted that presented data on influenza-related morbidity or mortality in groups with appropriate single vaccination and multiple vaccinations. "Appropriate vaccination" was defined as vaccination just before the influenza season wherein the outbreak under study occurred, in subjects who had not been vaccinated in the years before (single), or in subjects who also had been vaccinated in 1 or more consecutive years before (multiple). In the case of serologic studies, any article was accepted that included the sampling of 2 blood specimens, 1 before and a second 2 to 6 weeks after vaccination, in groups with single and multiple vaccinations. The assessment of serum antibody levels should have been done by a microtiter HI test. The most meaningful serologic variable is the postvaccination geometric mean antibody titer,[15] but virtually no article presented a measure of dispersion for these values, so that variable could not be used for a meta-analysis. Instead, we used the proportion of subjects exceeding a certain antibody titer threshold after vaccination, conventionally referred to as "serologic protection rate." Other commonly used variables, like mean fold increase or response rate, may show mathematical flaws[15] and were, therefore, not considered here.

Studies may contain 1 or more trials, according to the year of influenza outbreak and the subtypes involved (influenza A-H3N2, A-H1N1, and B). The individual trial was the unit of meta-analysis.

CALCULATIONS

Per trial, the difference between protection rates in groups with single (S) and multiple (M) vaccinations was calculated as follows: field protection-rate difference (PRD) = $(S_f/N_S - M_f/N_M) \times 100\%$, with N_S and N_M indicating the number of vaccinated subjects and S_f and M_f, the number of protected subjects after exposure (cases without influenza-related morbidity or mortality); and serologic PRD = $(S_s/N_S - M_s/N_M) \times 100\%$, with S_s and M_s indicating the number of subjects exceeding the protective antibody threshold after vaccination.

A PRD of greater than 0 favors single vaccination, and a PRD of less than 0 favors multiple vaccinations in preventing influenza infection after challenge (field protection) or in achieving high antibody titers after vaccination (serologic protection).

Protection-rate differences were subjected to meta-analysis according to Yusuf et al[16] (fixed-effects model) and DerSimonian and Laird[17] (random effects accounting for a possible heterogeneity of treatment effects). When a heterogeneity of treatment effects occurred, we first attempted to reduce the heterogeneity by forming subpopulations. The meta-analysis was repeated with odds ratios and relative risks to check the robustness of the pooled results in measuring effects. In some instances, more than 1 field or serologic trial within a study referred to identical groups of vaccinees. Therefore, a sensitivity analysis was performed by excluding the trials in question 1 at a time and observing whether the pooled result changed essentially.

For calculations, a software program (Meta-Analyst, version 0.991/1997) provided by Joseph Lau, MD, New England Medical Center, Boston, Mass, was used. The significance level for all calculations was .05.

tablished that a high serum antibody level can prevent infection.[12-14] It has, therefore, been widely accepted as a surrogate marker for protection against influenza and vaccine efficacy in serologic studies.

We attempted to identify all field and serologic influenza studies published during the past 3 decades that compare appropriate outcome measures in subjects vaccinated for the first time (single vaccination) with subjects vaccinated also in previous years (multiple vaccinations). Pooling of these data allows a quantitative analysis of whether the effect of influenza vaccination decreases when it is repeated annually.

RESULTS

FIELD STUDIES

Eight articles describing field studies were identified by the literature search and cross-references. One article, by Hoskins et al,[4] lacked appropriate groups with single and multiple vaccinations and was not included.[18] **Table 1** shows some relevant properties of the 7 remaining articles.[19-27] Nine trials were conducted in subjects of various age classes and different health states. "Influenza-related cases" were defined as incidents of influenzalike illness with or without laboratory confirmation in 6 articles[19-23,25] or as occurrences of death clinically related to influenza.[24] Two of the trials cumulated 3 observational years. The comparability of single- and multiple-vaccination groups in the risk of influenza-related morbidity (age, proven efficacy, and other factors) was controlled by a randomized study design in most articles.[20,21,23,25] In total, 13 influenza outbreaks occurred in 7355 subjects with single or multiple vaccinations (multiple counts of subjects allowed). Most outbreaks concerned influenza subtype A-H3N2. The antigenic match between the vaccine strain and the epidemic virus was excellent or sufficient in all outbreaks.

Table 1. Seven Field Studies of Influenza Vaccination

Article No.	Reference	Study Group, Age Range, y	Vaccine Type*	End Point (Case Definition)†	Season of Outbreak	Influenza Subtype	No. of Vaccinations‡
F-1	Hoskins et al,[20] 1973§	Boarding-school residents, 11-19	WV	Laboratory-confirmed ILI	1972-1973	A-H3N2	384
F-2	Hoskins et al,[19] 1976‖	Boarding-school residents, 11-19	WV	Laboratory-confirmed ILI	1973-1974	A-H3N2	169
F-3	Treanor et al,[21] 1992¶	Nursing-home residents, ≥65	SPL	Laboratory-confirmed ILI	1987-1988 to 1989-1990	A-H3N2	95
F-4	Govaert et al,[22] 1994#	Ambulatory elderly, 60-91	SPL	Laboratory-confirmed ILI	1991-1992	A-H3N2	918
F-5	Morio et al,[23] 1994**	School children NG	SPL	Clinical ILI	1989-1990 to 1991-1992	A-H3N2 A-H1N1	1619
F-6	Ahmed et al,[24] 1995††	Mostly elderly	NG	Influenza-related death	1989-1990	A-H3N2	235
F-7	Keitel et al,[25] 1997‡‡	Healthy adults	WV	Laboratory-confirmed ILI	A, 1983-1984	A-H1N1	300
					B, 1983-1984	B	300
					C, 1984-1985	A-H3N2	457
					D, 1985-1986	B	577
					E, 1986-1987	A-H1N1	723
					F, 1987-1988	A-H3N2	789
					G, 1987-1988	B	789

**WV indicates whole virus; SPL, split; and NG, not given.*
†ILI indicates influenzalike illness.
‡Total number of subjects with single vaccination and multiple vaccinations; multiple count allowed.
§A 3-year vaccination campaign and an influenza outbreak in the third year.
‖Continuation of the previous vaccination campaign for a fourth year with a mixed outbreak (influenza A and B). Data on the influenza A outbreak were derived from Hoskins et al.[4] Data on the influenza B outbreak could not be used because the study design did not provide a multiple-vaccination group.
¶Comparison of the efficacy of inactivated influenza vaccine only with inactivated influenza vaccine and with intranasal live attenuated influenza vaccine. Subgroups included here comprised subjects who had been immunized with inactivated vaccine only either twice (multiple vaccination) or once (single vaccination) before an outbreak of natural influenza A. Subgroups vaccinated also with live vaccine were not considered. The authors cumulated the observations of 3 influenza A-H3N2 outbreaks.
#A vaccination campaign and consecutive influenza outbreak. Two other articles describing the same study (Govaert et al[26,35]) did not use this case definition.
***A 3-year vaccination campaign. Incidences of ILI (not laboratory-confirmed) were recorded by questionnaire.*
††A case-control study of influenza-related death. See also discussion by Mühlemann and Weiss.[27]
‡‡A prospective study covering 5 influenza seasons. In 2 seasons (1983-1984 and 1987-1988), 2 different influenza subtypes circulated within the study group. These outbreaks were treated here as 2 independent events per season.

Table 2. Meta-analysis of 10 Field Trials

	Numbers†				Rate Differences‡
Trial*	N_S	S_f	N_M	M_f	fPRD (95% Confidence Interval)
F-2	125	121	44	39	8.2 (–1.7 to 18.0)
F-3	59	50	36	31	–1.4 (–15.9 to 13.2)
F-4	800	709	118	102	2.2 (–4.4 to 8.7)
F-7A	161	155	139	137	–2.3 (–5.8 to 1.2)
F-7B	161	158	139	134	1.7 (–2.0 to 5.5)
F-7C	172	164	285	276	–1.5 (–5.2 to 2.3)
F-7D	153	145	424	401	0.2 (–3.9 to 4.3)
F-7E	203	198	520	501	1.2 (–1.5 to 3.9)
F-7F	121	115	668	625	1.5 (–2.8 to –5.8)
F-7G	121	121	668	651	2.5 (0.9 to 4.2)
Pooled fPRD§	. . .	. . .	. . .	. . .	1.1 (–0.2 to 2.4)

**The numbers given to the trials refer to the article numbers in Table 1.*
† N_s and N_M indicate number of vaccinated subjects after single (S) or multiple (M) vaccination; S_f and M_f, number of protected subjects after exposure.
‡fPRD indicates field protection rate difference. Data are given as percentages.
§Ellipses indicate not applicable. Homogeneity statistic: $N_{total} = 51117$; $\chi^2_9 = 10.66$; $P = .30$.

Of 13 trials, 12 supported the hypothesis that annually repeated vaccination provides a protection at least as good as that of single vaccination, but 2 of them did not provide exact quantitative information needed for meta-analysis (F-1, F-5, Table 1), and for 1 trial (F-6, a case-control study), the analysis was made on the basis of odds ratios. On the remaining 10 trials with 5117 subjects, all using laboratory-confirmed influenzalike illness as the clinical end point, a meta-analysis was performed (**Table 2**). The test of heterogeneity showed that homogeneity among the trials could not be rejected ($P>.05$). The pooled field PDR was calculated as 1.1% (95% confidence interval, –0.2% to 2.4%; random-effects model), ie, multiple vaccination had no effect on the field protection rate. The result was similar when using the fixed-effects model or other effect measures or performing the sensitivity analysis as described in the "Calculations" subsection of the "Methods" section.

SEROLOGIC STUDIES

Twelve articles[5,28-38] presenting data on seroresponse after single and multiple vaccinations were identified (**Table 3**). Of 4 articles,[32,33,37,38] the original raw data were used. The articles covered 53 trials with 12 468 postvaccination titers (multiple counts allowed in subjects receiving bivalent or trivalent vaccines). All trials were performed in young or elderly adults or both. Vaccine doses were constant throughout the trials (10 or 15 µg of hemagglutinin per dose, except for 1 trial[28] wherein doses between 100 and 400 IU were used), but other details—health state, vaccine types, HI thresholds of subjects with

Table 3. Twelve Serologic Studies of Influenza Vaccination

Article No.	Reference	Age Range, y	Study Design (Years)[a]	Numbers			Vaccine Type[b]	HI Threshold[c]
				Relevant Years	Vaccine Components	Separate Trials		
S-1	Howells et al,[28] 1975[d]	>61	Cohort (1971-1973)	2	2	4	WV	10
S-2	Powers et al,[29] 1984[e]	18-65	Cohort (1981-1982)	1	3	3	WV	40
S-3	Keitel et al,[5] 1988[f]	30-60	Cohort (1983-1985)	2	3	6	WV	32
S-4	Peters et al,[30] 1988[g]	70-96	1 year (1985)	1	1	1	WV	32
S-5	Gross et al,[31] 1989[h]	60-91	1 year (1986)	1	3	3	SPL	40
S-6	Beyer et al,[32] 1990[i]	18-84	1 year (1987)	1	3	3	WV	100/200
S-7	McElhaney et al,[33] 1993[j]	22-85	1 year (1990,1991)	2	3	6	WV, SPL	40
S-8	Glathe et al,[34] 1993[k]	Adults	1 year (1991)	1	3	3	SPL	40
S-9	Govaert et al,[35] 1994[l]	60-91	1 year (1991)	1	3	3	SPL	100/200
S-10	Pyhälä et al,[36] 1994[m]	25-57	Cohort (1990-1992)	2	3	6	SPL	40
S-11	Beyer et al,[37] 1996[n]	18-98	Cohort (1986-1989)	3	3	9	SU,WV	40 100/200
S-12	de Bruijn et al,[38] 1997[o]	18-82	Cohort (1990-1993)	2	3	6	SU	100/200

[a] *Cohort indicates study during several years with new entries in consecutive years; 1 year, a single study with known vaccination history of the previous year.*
[b] *WV indicates whole virus; SPL, split; and SU, subunit.*
[c] *Threshold to identify subjects with high ("protective") hemagglutination-inhibition (HI) titers.*
[d] *Numbers of new entries and of revaccinated subjects were derived from Table 1 (total) and protection rates from Table 2 of the article (1972: A [H/K] 68 and B; 1973: A [42/72] and B).*
[e] *Study subjects were immunized up to 3 times with time intervals of 6 months. Data are estimated from Figures 1 and 2 of the article, with "2nd vaccination group A" (Figure 1) as multiple-vaccinations group and "1st vaccination group B" (Figure 2) as single-vaccination group.*
[f] *Data are derived from Tables 1 and 2 of the article.*
[g] *Information on the effect of previous vaccination was given for the influenza B vaccine component but not for the influenza A components.*
[h] *Data are derived from Table 3 of the article. Data on a smaller group receiving also A-Taiwan-1-86 (H1N1) 1 month later are not included.*
[i] *Data on the effect of previous vaccinations are presented as "mean fold increase." Original raw data have been reanalyzed.*
[j] *Discrimination between previously unvaccinated and vaccinated subjects was possible through original raw data (provided by Janet E. McElhaney, MD, PhD).*
[k] *Five groups of young and elderly adults with different proportions of previous vaccinations were studied. The authors did not perform a statistical analysis on the effect of previous vaccination through the study groups. Data are derived from Tables 2 to 4, with "Group A" (not previously vaccinated subjects; mean age, 28 years) as the single-vaccination group and "Group E" (95% previously vaccinated; mean age, 80 years) as the multiple-vaccinations group. An age bias cannot be excluded.*
[l] *Data are derived from Table 3 (prevaccination and postvaccination protection rates for B-Panama-45-90 exchanged). Data on the second B strain (B-Beijing-1-87) are not included.*
[m] *Data are estimated from Figure 2, with "group 1" as multiple-vaccinations group and "group 2" as the single-vaccination group in 1991 and "group 1" and "group 2" (pooled) as multiple-vaccinations group and "group 3" as single vaccination group in 1992. Calculations are based on data for A-Beijing-353-89 (H3N2), A-Finland-164-91 (H1N1), and B-Yamagata-16-88.*
[n] *Three cohort studies in young and elderly adults were pooled by year. Data are derived from Figure 1.2 in the article by Beyer et al[37] and controlled by available raw data.*
[o] *For 1991 and 1992, subjects with single vaccination could be compared with those with multiple vaccinations.*

high titers—varied considerably among studies. Hemagglutination-inhibition tests were performed by either methods similar to those described by Dowdle et al[39] (Keitel,[5] Howells,[28] Powers,[29] Peters,[30] Gross,[31] McElhaney,[33] Glathe,[34] Pyhälä,[36] and their colleagues) or the method of Masurel et al[40] and Beyer et al[41] (Beyer,[32,37] Govaert,[35] de Bruijn,[38] and their associates).

Of all 53 trials, 44 (83%) supported the working hypothesis that multiple vaccinations provided a protection at least as good as that of single vaccination, and 9 did not. One trial (S-4, n = 129) (Table 3) that did not support the working hypothesis presented geometric mean antibody titers only, and no serologic PRDs could be calculated. **Table 4** shows the results for the remaining 52 trials. The serologic PRDs varied in a large range around 0 (–25.4% to 26.6%). Eight serologic PRDs were significantly greater than 0, and 7 were significantly less than 0. The estimated pooled rate difference was close to 0: 1.7% (95% confidence interval, –1.3% to 4.8%; random-effects model) or 0.8% (95% confidence interval, –0.4% to 1.9%; fixed-effects model). This result should be interpreted with caution because it was based, in part, on multiple observations (the same volunteers were vaccinated with bivalent or trivalent vaccines, producing 2 or 3 results per trial), and the test of heterogeneity clearly indicated the absence of homogeneity between trials ($P<.001$). Subdividing according to influenza subtypes suggested slight differences between A-H3N2 (pooled rate difference <0) and A-H1N1 and B (pooled rate difference >0) and did not reduce heterogeneity. Similarly, subdividing according to age classes (younger adults vs elderly), study design types (cohort vs 1-year design), HI assay methods, or vaccine types (not shown) did not reduce heterogeneity. On the other hand, robustness and sensitivity analysis did not reveal any essential changes of the result. Therefore, the true pooled serologic PRD, despite considerable heterogeneity between trials, is close to 0, and there is no evidence for assuming a generally lower seroresponse of annually vaccinated subjects than that of subjects vaccinated for the first time.

COMMENT

The state of previous vaccination does not influence field or serologic protection against influenza. Concerns about a decreasing field protection after a number of annual vac-

Table 4. Meta-analysis of 52 Serologic Trials of Influenza Vaccination

Trial No.	Vaccine Subtype	Numbers* N_S	S_s	N_M	M_s	Rate Differences† sPRD (95% Confidence Interval)
S-1A	A-H3N2	123	89	134	103	−4.5 (−15.2 to 6.1)
	B	123	63	134	44	18.4 (6.5 to 30.3)
S-1B	A-H3N2	183	181	257	257	−1.1 (−2.9 to 0.7)
	B	183	143	257	234	−12.9 (−19.8 to −6.0)
S-2	A-H3N2	35	34	26	23	8.7 (−4.8 to 22.1)
	A-H1N1	35	30	26	24	−6.6 (−22.1 to 8.9)
	B	35	34	26	24	4.8 (−6.8 to 16.5)
S-3A	A-H3N2	167	78	142	64	1.6 (−9.5 to 12.8)
	A-H1N1	168	148	148	129	0.9 (−6.3 to 8.2)
	B	168	35	148	19	8.0 (−0.2 to 16.2)
S-3B	A-H3N2	168	79	289	116	6.9 (−2.5 to 16.3)
	A-H1N1	173	107	287	149	9.9 (0.7 to 19.2)
	B	173	9	288	6	3.1 (−0.6 to 6.8)
S-5	A-H3N2	27	18	113	76	−0.6 (−20.4 to 19.2)
	A-H1N1	27	18	113	64	10.0 (−10.0 to 30.0)
	B	27	20	113	82	1.5 (−17.0 to 20.0)
S-6	A-H3N2	65	31	41	16	8.7 (−10.6 to 27.9)
	A-H1N1	65	21	41	11	5.5 (−12.2 to 23.2)
	B	65	26	41	8	20.5 (3.5 to 37.5)
S-7A	A-H3N2	16	11	9	6	2.1 (−36.2 to 40.4)
	A-H1N1	16	8	9	5	−5.6 (−46.2 to 35.1)
	B	17	8	9	2	24.8 (−11.2 to 60.9)
S-7B	A-H3N2	28	7	24	3	12.5 (−8.3 to 33.3)
	A-H1N1	28	8	24	7	−0.6 (−25.3 to 24.1)
	B	28	1	24	2	−4.8 (−17.8 to 8.3)
S-8	A-H3N2	34	29	58	58	−14.7 (−27.0 to −2.4)
	A-H1N1	34	27	58	56	−17.1 (−31.5 to −2.8)
	B	34	31	58	56	−5.4 (−16.0 to 5.2)
S-9	A-H3N2	788	552	118	61	18.4 (8.8 to 27.9)
	A-H1N1	788	370	118	24	26.6 (18.6 to 34.7)
	B	788	402	118	44	13.7 (4.3 to 23.1)
S-10A	A-H3N2	9	7	24	17	6.9 (−25.7 to 39.6)
	A-H1N1	9	8	24	21	1.4 (−23.0 to 25.8)
	B	9	7	24	19	−1.4 (−33.0 to 30.3)
S-10B	A-H3N2	12	10	33	28	−1.5 (−25.9 to 22.9)
	A-H1N1	12	11	33	28	6.8 (−13.0 to 26.7)
	B	12	10	33	25	7.6 (−18.1 to 33.2)
S-11A	A-H3N2	124	88	291	258	−17.7 (−26.5 to −8.9)
	A-H1N1	124	80	291	185	0.9 (−9.1 to 11.0)
	B	124	86	291	197	1.7 (−8.1 to 11.4)
S-11B	A-H3N2	157	106	271	199	−5.9 (−14.9 to 3.1)
	A-H1N1	157	82	271	125	6.1 (−3.7 to 15.9)
	B	157	104	271	132	17.5 (8.0 to 27.0)
S-11C	A-H3N2	105	58	171	99	−2.7 (−14.7 to 9.4)
	A-H1N1	105	55	171	77	7.4 (−4.8 to 19.5)
	B	105	40	171	50	8.9 (−2.7 to 20.4)
S-12A	A-H3N2	97	65	58	45	−10.6 (−24.8 to 3.7)
	A-H1N1	97	30	58	22	−7.0 (−22.5 to 8.5)
	B	97	61	58	39	−25.4 (−38.0 to 12.9)
S-12B	A-H3N2	64	44	77	68	−19.6 (−33.0 to −6.1)
	A-H1N1	64	38	77	28	23.0 (6.9 to 39.1)
	B	64	30	77	55	−24.6 (−40.4 to −8.7)
Pooled sPRD						1.7 (−1.3 to 4.8)
Homogeneity statistic		N_{total} = 12 341; χ^2_{51} = 207.5; P<.001				
A-H3N2: Pooled sPRD						−1.7 (−6.3 to 2.9)
Homogeneity statistic		N_{total} = 4338; χ^2_{17} = 52.6; P<.001				
A-H1N1: Pooled sPRD						4.8 (−1.3 to 11.0)
Homogeneity statistic		N_{total} = 3651; χ^2_{15} = 49.0; P<.001				
B: Pooled sPRD						2.4 (−3.4 to 8.1)
Homogeneity statistic		N_{total} = 4352; χ^2_{17} = 83.6; P<.001				

*N_S and N_M indicate the number of vaccinated subjects after single (S) or multiple (M) vaccination; S_s and M_s, the number of protected subjects after exposure.

†sPRD indicates serologic protection rate difference.

cinations, as expressed by Hoskins et al,[4] could not be substantiated in a review of 7 articles involving 13 field trials in a total of 7355 vaccinees. Of these 13 field trials, 10 could be subjected to a meta-analysis because they had been based on the same clinical case definition (influenza-related morbidity, ie, clinical influenzalike illness confirmed by laboratory means). These trials showed a sufficient intertrial homogeneity (P = .30, Table 2) and produced a pooled field PRD virtually equal to 0 (ie, no difference in field protection between groups with single and multiple vaccination). This result remained stable in robustness and sensitivity analyses. A selection bias that may have influenced the change of a vaccinee to receive either single or multiple vaccination could not be detected.

Of 53 serologic trials with 12 468 observations in 12 articles, 44 (83%) confirmed the results of the field studies. Fifty-two trials could be subjected to meta-analysis that, again, produced an overall PRD virtually equal to 0. However, the interpretation of this result deserves comment. The total range of serologic PRDs and the 95% confidence intervals of most individual serologic PRDs were large. Several trials even "contradicted" each other by significantly favoring either single vaccination or multiple vaccinations (Table 4). Considerable heterogeneity of treatment effects was present. This variability between serologic studies is well known and has been described earlier.[11,37,42,43] Although the postvaccination HI titer is a valuable surrogate marker for real protection, it may depend on a number of cofactors that are imperfectly controlled by the study design, among others, prevaccination titer and study population characteristics (age; history of previous exposure to natural influenza, especially the effect of the "original antigenic sin"[44]; health state; etc).

The present heterogeneity among serologic studies does not argue against our conclusion that repeated vaccination is not associated with a decrease in effectiveness. The pooled serologic PRD (calculated by a meta-analysis method that accounts for heterogeneity) and the huge majority of individual serologic trials did not detect any meaningful difference between groups of single and multiple vaccinations. This accords with the results of the field studies and may be taken as additional evidence that annual influenza vaccination does not affect vaccine-provided protection against natural influenza.

On the other hand, large heterogeneity among serologic studies is undesirable and should stimulate further efforts to standardize study designs between study centers. The HI test should be standardized among laboratories, eg, by introducing internationally accepted reference serum, and the end points of serologic studies should be predetermined.[15] In particular, the state of previous vaccination, besides the prevaccination titer,[37] should be included as a possible source of effect modification in the statistical analysis of influenza vaccine trials. It could be shown (Table 4) that in several individual trials, the state of previous vaccination was indeed a significant confounder, although its general effect was virtually 0.

For the past 20 years, the articles by Hoskins et al[4,19,20] have caused doubts about the common policy of

vaccinating populations at risk on an annual basis (the Hoskins paradox). Their results can be disputed, particularly because of serious shortcomings in study design. Hoskins et al[4] described a vaccination campaign in adolescents and 4 influenza outbreaks from 1970 to 1976. During the first outbreak in 1972-1973 (influenza A-H3N2), no adverse effect of repeated vaccination could be detected (see also Table 1, F-1), but exact data were not given. During the second outbreak in 1973-1974 (influenza A-H3N2), the attack rate was indeed higher in groups with multiple vaccinations than in those with single vaccination, but the difference was not significant (F-2, Tables 1 and 2). A simultaneous influenza B outbreak could not be evaluated because of the lack of a group with multiple vaccinations. The last influenza A outbreak in 1975-1976 also lacked an appropriate group with multiple vaccinations. In conclusion, the Hoskins paradox cannot be substantiated by Hoskins's own data.[18]

Taken together with the results of this review, the Hoskins paradox has no basis in reality and should not influence the decision whether to consider annual influenza vaccination.

Another clinically relevant issue is whether there may be differences between vaccine-related reactions or adverse events between the first and annually repeated vaccinations. In the articles reviewed here, no such data were given. In a previous article,[45] no such differences were found in 1800 adult vaccinees (16-94 years of age). Thus, it appears that the current inactivated influenza vaccines are safe and well tolerated when used annually.

Accepted for publication April 13, 1998.

This study was supported by the Foundation of Respiratory Virology, notably Influenza, Rotterdam, the Netherlands.

We thank Janet E. McElhaney, MD, PhD, Edmonton, Alberta, for kindly providing original data; Nic Masurel, MD, PhD, Leiden, Jan C. de Jong, MSc, PhD, Bilthoven, and Rob Diepersloot, MD, PhD, Utrecht, the Netherlands, for their valuable comments; and Conny Kruyssen for help in preparing the manuscript.

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