



Original Contribution

Safety of MF59-Adjuvanted Influenza Vaccination in the Elderly: Results of a Comparative Study of MF59-Adjuvanted Vaccine Versus Nonadjuvanted Influenza Vaccine in Northern Italy

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MF59-adjuvanted trivalent influenza vaccine (Novartis Vaccines and Diagnostics, Siena, Italy) has been shown to be more effective than nonadjuvanted vaccine in the elderly population. Here we present results from a large-scale, observational, noninterventional, prospective postlicensure study that evaluated the safety of MF59-adjuvanted vaccine in elderly subjects aged 65 years or more. The study was performed in 5 northern Italian health districts during the 2006–2007, 2007–2008, and 2008–2009 influenza seasons. The choice of vaccine—either adjuvanted vaccine or a nonadjuvanted influenza vaccine—was determined by individual providers on the basis of local influenza vaccination policy. Hospitalizations for potential adverse events of special interest (AESIs) were identified from hospital databases and then reviewed against recognized case definitions to identify confirmed cases of AESI. Cumulative incidences were calculated for AESIs in predefined biologically plausible time windows, as well as in a 6-month window following vaccination. During the 3-year study period, 170,988 vaccine doses were administered to a total of 107,661 persons. Despite the large study size, cases of AESI resulting in hospitalization were rare, and risks of AESI were similar in both the MF59-adjuvanted and nonadjuvanted vaccination groups. In conclusion, similar safety profiles were observed for both nonadjuvanted and MF59-adjuvanted seasonal influenza vaccines in elderly recipients.

adjuvants; elderly; influenza; influenza vaccine; MF59; vaccines; vaccine safety

Abbreviations: AESI, adverse event of special interest; ATIV, adjuvanted trivalent influenza vaccine; ICD-9, *International Classification of Diseases, Ninth Revision*; LIVE, Lombardia Influenza Vaccine Effectiveness; TIV, trivalent influenza vaccine.

Influenza infection is a major cause of illness, morbidity, and mortality throughout the world. The World Health Organization has estimated that influenza affects 5%–15% of the global population each year (1). Groups at high risk for influenza complications include the elderly, patients with chronic pulmonary and cardiovascular conditions, and institutionalized persons such as people in nursing homes (2). While routine influenza vaccination of the elderly is supported by clinical and economic evidence of its effectiveness in reducing morbidity and mortality (3), several studies have shown that the effectiveness of vaccination is not optimal, ranging from 30% to 70% in preventing hospitalization for pneumonia (4).

Observational studies in nursing home residents have shown 50%–60% effectiveness (5). Part of the explanation for this sub-optimal level of effectiveness is immunosenescence, which leads to lower immunogenicity of nonadjuvanted influenza vaccines in the elderly as compared with young adults (6). To address this issue, adjuvanted influenza vaccines have been developed. The MF59-adjuvanted trivalent influenza vaccine (ATIV) Fluvad (Novartis Vaccines and Diagnostics, Siena, Italy) has been in use in Europe since 1997, with more than 50 million doses having been administered. Several studies have shown that this vaccine provides improved immunogenicity as well as broader protection against heterosubtypic or

antigenically drifted strains of influenza in comparison with nonadjuvanted trivalent influenza vaccine (TIV) (7).

While reports from clinical studies and passive surveillance systems in several countries have shown this vaccine to be safe and well tolerated, a large prospective systematic assessment of safety in the elderly has not been performed. Here we report results from such an assessment, a study conducted among elderly adults (ages ≥ 65 years) in the northern Italian region of Lombardy.

MATERIALS AND METHODS

The Lombardia Influenza Vaccine Effectiveness (LIVE) Study (8) was an observational, noninterventional, prospective cohort study performed in the Italian local health authorities of Cremona, Mantova, Pavia, Lecco, and Bergamo during the 2006–2007, 2007–2008, and 2008–2009 influenza seasons to compare the effectiveness of the ATIV, Flud, and a nonadjuvanted TIV, Agrippal (Novartis Vaccines and Diagnostics). The current safety evaluation was a secondary objective of the LIVE Study. The study location was chosen because of the highly developed computerized clinical information systems available in the Lombardy region and the considerable experience with performing pharmacoepidemiologic studies in this population.

Residents aged ≥ 65 years seeking influenza vaccination at local health authorities' district offices or the offices of participating general practitioners were eligible for enrollment. Subjects who were currently institutionalized or had been in a nursing or rehabilitation center within 30 days before the start of the study were excluded. Eligible subjects were informed by the vaccinators about the study and asked for their consent to participate. The assignment of ATIV or TIV was determined by the individual providers in conformance with local influenza vaccination policy. According to Italian guidelines, adjuvanted vaccine was preferentially recommended for elderly persons with underlying chronic conditions. This was a 3-year study, and participants could be enrolled for multiple years. All study participants were provided with a brief questionnaire on basic medical history, smoking status, functional status, and influenza vaccination history for the prior year. The type of vaccine received was recorded in the study database. More details about the operational procedures of the LIVE Study are provided elsewhere (8).

Using lists of serious safety outcomes developed by the US Food and Drug Administration, the European Centre for Disease Control, and the World Health Organization to assess the safety of the influenza vaccines, we developed a prespecified list of adverse events of special interest (AESIs) (9). To increase case ascertainment, we used a broad list of *International Classification of Diseases, Ninth Revision* (ICD-9), codes that were designed to be sensitive rather than specific (Appendix Table 1). Using a patient identifier (the Italian National Fiscal Code) unique to each person receiving care within the Italian health-care system, all hospitalizations with any of the listed ICD-9 codes occurring before or during the study period were identified. All potential cases underwent clinical validation. Brighton Collaboration definitions and classification

schemes (<https://brightoncollaboration.org/public/what-we-do/setting-standards/guidelines.html>) were used preferentially when available; when they were not available, recognized classification schemes developed by national specialty organizations were used (Appendix Table 2).

Clinical validation of all potential cases of AESI identified through record linkage was performed according to a predefined validation plan and was managed by the coordinating study center (the Cremona Local Health Authority). The Cremona Local Health Authority requested and obtained paper copies of patients' medical charts from all hospitals identified by record linkage as having discharged study subjects with a diagnosis code for an AESI. Depending on the type of AESI experienced, the medical charts (blinded with respect to subjects' identity, condition, and time of vaccination) were examined by one of 2 independent teams of medical experts, one for immunology-related AESIs and one for neurological events. The medical teams convened to evaluate the cases according to their areas of expertise at the premises of the Cremona Local Health Authority. The immunology team included 2 medical experts. The first expert examined the clinical documentation received from the hospitals and expressed his opinion on each case, while the second reviewed the validation performed by his colleague and had the ultimate responsibility for deciding the final adjudication category, which was either "definite," "probable," "possible," "cannot be ruled out," or "ruled out." Similarly, the medical team responsible for neurological events included 3 experts, 2 of whom performed the initial clinical validation, while the third was in charge of the final adjudication. The development of the validation protocol was performed by RTI Health Solutions (Research Triangle Park, North Carolina). The reviewers and adjudicators were all expert physicians from academic institutions.

According to a prespecified analysis plan, the primary analysis for each AESI involved calculating the cumulative incidence, as well as the risk difference and binomial exact 95% confidence interval, for new-onset cases classified as either "definite," "probable," or "possible," that occurred during the biologically plausible time window for each outcome, as defined by the World Health Organization, the US Food and Drug Administration, and the European Centre for Disease Control. An additional secondary analysis was performed for similarly confirmed hospitalizations occurring within 6 months of vaccination. For each of these time frames, secondary sensitivity analyses were performed that included cases for the outcome classified as "cannot be ruled out," in addition to the "definite," "probable," or "possible" cases.

Since hospital coding often includes diagnostic codes for chronic conditions that may not have been a cause of acute hospitalization or may not be currently active conditions, for the chronic conditions of Bell's palsy, encephalitis, vasculitis, Guillain-Barré syndrome, acute transverse myelitis, demyelinating disease, and optic neuritis, only cases without a history of a hospitalization for the same condition within the past 3 months were included as incident cases in the analyses. For anaphylaxis and convulsions, all events were included regardless of prior history.

Table 1. Characteristics of Vaccinees Aged ≥ 65 Years at Enrollment in the Lombardia Influenza Vaccine Effectiveness Study, by Type of Vaccine Received, Lombardy, Italy, 2006–2009

Characteristic	Vaccine	
	ATIV	TIV
Mean age, years	76.5	74.9
Chronic disease, %		
Chronic obstructive pulmonary disease	11.9	10.4
History of pneumonia, influenza, or emphysema	3.0	2.3
Chronic kidney disease	0.9	0.7
Cancer	15.1	14.2
Diabetes	15.9	15.0
Heart disease	75.1	72.1
Vascular disease	7.2	6.1
Functional limitation in daily activities, %		
Severe	16.9	12.3
Mild	30.5	27.1
None	52.6	60.6
Functional limitation in climbing stairs, %		
Severe	17.3	12.8
Mild	32.8	29.6
None	49.9	57.6

Abbreviations: ATIV, adjuvanted trivalent inactivated vaccine; TIV, trivalent inactivated vaccine.

RESULTS

During the 3 study years, 170,988 vaccine doses (88,449 ATIV; 82,539 TIV) were administered to 107,661 study participants. The 2 vaccine groups showed some imbalance with respect to age, functional limitations, and prevalence of chronic conditions (Table 1). Linkage of the study database to the medical records hospitalization database revealed that 460

Table 2. Numbers of Hospitalizations Occurring in the Biologically Plausible Time Windows and the 6-Month Time Window Following Vaccination Among Vaccinees Aged ≥ 65 Years, Lombardy, Italy, 2006–2009

Outcome	Biologically Plausible Time Windows	6-Month Time Window
Anaphylaxis	1	33
Autoimmune hepatitis	4	19
Bell's palsy	1	8
Convulsions	14	189
Demyelinating disorders	4	16
Encephalitis	0	1
Guillain-Barré syndrome	15	96
Immune thrombocytopenic purpura	13	59
Vasculitis	6	39
Total	58	460

hospitalizations in 401 subjects were coded with an ICD-9 code of potential AESI during the 6-month time window; 58 hospitalizations in 56 subjects occurred within the predefined biologically plausible windows. Table 2 shows the distribution of such potential cases. The positive predictive value (i.e., the percentage of cases actually confirmed as having the outcome of interest out of the total number of potential cases) of the ICD-9 code search of the medical records varied between 3% for anaphylaxis to 100% for encephalitis, with the ICD-9 code lists for many outcomes having positive predictive values of less than 50%, thus confirming the need for case adjudication.

The results of the primary and secondary analyses for the 2 time windows (biologically plausible and 6 months) are shown in Tables 3–6. In the primary analysis for the biologically plausible time windows (Table 3), there were no validated events observed for Guillain-Barré syndrome, anaphylaxis, autoimmune hepatitis, demyelinating disease, or encephalitis.

Table 3. Numbers of “Definite,” “Probable,” and “Possible” Cases of Adverse Events of Special Interest Arising During the Biologically Plausible Time Windows Following Receipt of ATIV ($n = 88,449$) and TIV ($n = 82,539$) Among Vaccinees Aged ≥ 65 Years (Primary Analysis), Lombardy, Italy, 2006–2009

Outcome	TIV			ATIV			Difference	
	No. of Cases	Risk ^a	95% CI	No. of Cases	Risk ^a	95% CI	Risk ^a	95% CI
Anaphylaxis	0	0.00	0.00, 4.47	0	0.00	0.00, 4.17	0.00	N/A
Autoimmune hepatitis	0	0.00	0.00, 4.47	0	0.00	0.00, 4.17	0.00	N/A
Bell's palsy	0	0.00	0.00, 4.47	1	1.13	0.03, 6.30	1.13	-1.09, 3.35
Convulsions	6	7.27	2.67, 15.82	4	4.52	1.23, 11.58	-2.75	-10.06, 4.57
Demyelinating disorders	0	0.00	0.00, 4.47	0	0.00	0.00, 4.17	0.00	N/A
Encephalitis	0	0.00	0.00, 4.47	0	0.00	0.00, 4.17	0.00	N/A
Guillain-Barré syndrome	0	0.00	0.00, 4.47	0	0.00	0.00, 4.17	0.00	N/A
Immune thrombocytopenic purpura	1	1.21	0.03, 6.75	2	2.26	0.27, 8.17	1.05	-2.88, 4.98
Vasculitis	0	0.00	0.00, 4.47	2	2.26	0.27, 8.17	2.26	-0.87, 5.39

Abbreviations: ATIV, adjuvanted trivalent inactivated vaccine; CI, confidence interval; N/A, not available; TIV, trivalent inactivated vaccine.

^a Cumulative incidence (number of cases per 100,000 persons).

Table 4. Numbers of “Definite,” “Probable,” and “Possible” Cases of Adverse Events of Special Interest Arising During the 6-Month Time Window Following Receipt of ATIV ($n = 88,449$) and TIV ($n = 82,539$) Among Vaccinees Aged ≥ 65 Years (Secondary Analysis), Lombardy, Italy, 2006–2009

Outcome	TIV			ATIV			Difference	
	No. of Cases	Risk ^a	95% CI	No. of Cases	Risk ^a	95% CI	Risk ^a	95% CI
Anaphylaxis	0	0.00	0.00, 4.47	1	1.13	0.00, 6.30	1.13	-1.09, 3.35
Autoimmune hepatitis	0	0.00	0.00, 4.47	0	0.00	0.00, 4.17	0.00	N/A
Bell's palsy	1	1.21	0.03, 6.75	2	2.26	0.27, 8.17	1.05	-2.88, 4.98
Convulsions	41	49.67	35.65, 67.39	39	44.09	31.36, 60.27	-5.58	-26.12, 14.97
Demyelinating disorders	0	0.00	0.00, 4.47	0	0.00	0.00, 4.17	0.00	N/A
Encephalitis	1	1.21	0.03, 6.75	0	0.00	0.00, 4.17	-1.21	-3.59, 1.16
Guillain-Barré syndrome	4	4.85	1.32, 12.41	1	1.13	0.03, 6.30	-3.72	-8.96, 1.53
Immune thrombocytopenic purpura	1	1.21	0.03, 6.75	3	3.39	0.70, 9.91	2.18	-2.33, 6.69
Vasculitis	1	1.21	0.03, 6.75	5	5.65	1.84, 13.19	4.44	-1.05, 9.94

Abbreviations: ATIV, adjuvanted trivalent inactivated vaccine; CI, confidence interval; N/A, not available; TIV, trivalent inactivated vaccine.

^a Cumulative incidence (number of cases per 100,000 persons).

There was 1 case of Bell's palsy in the ATIV group versus no cases in the TIV group, 4 cases of convulsions in the ATIV group versus 6 in the TIV group, 2 cases of immune thrombocytopenic purpura in the ATIV group versus 1 in the TIV group, and 2 cases of vasculitis in the ATIV group versus none in the TIV group. In the secondary analysis, performed using the 6-month exposure window following vaccination (Table 4), larger numbers of events were observed, notably for convulsions. Cases of Guillain-Barré syndrome and convulsion were more common in the TIV group in this analysis, whereas there were more cases of immune thrombocytopenic purpura in the ATIV group.

In the sensitivity analyses, which incorporated cases for each outcome that had been classified as “cannot rule out,” the number of events in the analyses increased as expected, both in the biologically plausible time windows (Table 5) and in the 6-month time window (Table 6), but there was no indication of any adverse effect among the studied endpoints that emerged with the addition of these borderline cases.

Despite the large size of the 2 vaccine cohorts, hospitalization for any of the AESIs, except for convulsion, was rare in both groups. Risks of AESI were similar in the ATIV and TIV groups. Overall, there was no indication that receipt of MF59-adjuvanted vaccine was associated with an increased risk of any AESI.

DISCUSSION

To our knowledge, this was the first large prospective postlicensure study to evaluate the safety of ATIV in the elderly. Observational studies based on automated data offer distinct advantages over passive surveillance in that outcomes are systematically and efficiently ascertained, with very limited potential for loss of outcome events leading to hospitalization. In our case, since all hospitalizations of subjects registered with the local health authorities are included in the database, we can be confident that all such events were identified. In addition, there was no risk of preferential self-reporting for

Table 5. Numbers of “Definite,” “Probable,” “Possible,” and “Cannot Be Ruled Out” Cases of Adverse Events of Special Interest Arising During the Biologically Plausible Time Windows Following Receipt of ATIV ($n = 88,449$) and TIV ($n = 82,539$) Among Vaccinees Aged ≥ 65 Years (Secondary Sensitivity Analysis), Lombardy, Italy, 2006–2009

Outcome	TIV			ATIV			Difference	
	No. of Cases	Risk ^a	95% CI	No. of Cases	Risk ^a	95% CI	Risk ^a	95% CI
Anaphylaxis	0	0.00	0.00, 4.47	0	0.00	0.00, 4.17	0.00	N/A
Autoimmune hepatitis	0	0.00	0.00, 4.47	0	0.00	0.00, 4.17	0.00	N/A
Bell's palsy	0	0.00	0.00, 4.47	1	1.13	0.03, 6.30	1.13	-1.09, 3.35
Convulsions	7	8.48	3.41, 17.47	4	4.52	1.23, 11.58	-3.96	-11.65, 3.73
Demyelinating disorders	0	0.00	0.00, 4.47	0	0.00	0.00, 4.17	0.00	N/A
Encephalitis	0	0.00	0.00, 4.47	0	0.00	0.00, 4.17	0.00	N/A
Guillain-Barré syndrome	0	0.00	0.00, 4.47	0	0.00	0.00, 4.17	0.00	N/A
Immune thrombocytopenic purpura	3	3.63	0.75, 10.62	4	4.52	1.23, 11.58	0.89	-5.16, 6.93
Vasculitis	0	0.00	0.00, 4.47	3	3.39	0.70, 9.91	3.39	-0.45, 7.23

Abbreviations: ATIV, adjuvanted trivalent inactivated vaccine; CI, confidence interval; N/A, not available; TIV, trivalent inactivated vaccine.

^a Cumulative incidence (number of cases per 100,000 persons).

Table 6. Numbers of “Definite,” “Probable,” “Possible,” and “Cannot Be Ruled Out” Cases of Adverse Events of Special Interest Arising During the 6-Month Time Window Following Receipt of ATIV ($n = 88,449$) and TIV ($n = 82,539$) Among Vaccinees Aged ≥ 65 Years (Secondary Sensitivity Analysis), Lombardy, Italy, 2006–2009

Outcome	TIV			ATIV			Difference	
	No. of Cases	Risk ^a	95% CI	No. of Cases	Risk ^a	95% CI	Risk ^a	95% CI
Anaphylaxis	7	8.48	3.41, 17.47	5	5.65	1.84, 13.19	-2.83	-10.83, 5.17
Autoimmune hepatitis	1	1.21	0.03, 6.75	0	0.00	0.00, 4.17	-1.21	-3.59, 1.16
Bell's palsy	2	2.42	0.29, 8.75	2	2.26	0.27, 8.17	-0.16	-4.75, 4.43
Convulsions	51	61.79	46.01, 81.23	47	53.14	39.05, 70.66	-8.65	-31.39, 14.11
Demyelinating disorders	0	0.00	0.00, 4.47	0	0.00	0.00, 4.17	0.00	N/A
Encephalitis	1	1.21	0.03, 6.75	0	0.00	0.00, 4.17	-1.21	-3.59, 1.16
Guillain-Barré syndrome	5	6.06	1.97, 14.14	2	2.26	0.27, 8.17	-3.80	-9.96, 2.37
Immune thrombocytopenic purpura	10	12.12	5.81, 22.28	6	6.78	2.49, 14.76	-5.33	-14.59, 3.93
Vasculitis	4	4.85	1.32, 12.41	12	13.57	7.01, 23.70	8.72	-0.31, 17.74

Abbreviations: ATIV, adjuvanted trivalent inactivated vaccine; CI, confidence interval; N/A, not available; TIV, trivalent inactivated vaccine.

^a Cumulative incidence (number of cases per 100,000 persons).

one group or the other; conversely, there may have been a higher risk of incidental ascertainment of outcome events in the ATIV group, which was more frail and therefore more likely to be hospitalized independently of AESI.

This study was performed in a population where persons with chronic conditions and those who were considered fragile were more likely to receive adjuvanted influenza vaccine; choice of vaccine was not random, and higher-risk patients were preferentially vaccinated with adjuvanted vaccine. Thus, ATIV recipients were more likely to have chronic conditions or to be generally fragile and were therefore more likely to be hospitalized. Despite this, the study generated no evidence to suggest that the ATIV group had a higher risk of AESIs when compared with the TIV group.

A limitation in the design of this study was its reliance on hospitalization events as the endpoint of interest. Less clinically significant adverse events—that is, minor events that might result in ambulatory visits but would not result in hospitalization—were not assessed in this study. Because this was a prospective cohort study with complete case ascertainment for hospitalizations and subsequent validation, in each vaccine cohort we were also able to calculate cumulative incidences for these events. Rates for all AESIs in this study were consistent with or lower than reported population-based background rates from other studies (9). These findings support existing data from clinical studies and passive safety reporting (10, 11). Altogether, data from this study indicate that MF59-adjuvanted vaccine has a safety profile similar to that of nonadjuvanted vaccine in an elderly population.

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(Appendix follows)

Appendix Table 1. *International Classification of Diseases, Ninth Revision, Codes Used to Identify Potential Cases and Biologically Plausible Time Windows for Predefined Adverse Events of Special Interest Among Vaccinees Aged ≥65 Years, Lombardy, Italy, 2006–2009*

Outcome	ICD-9 Code(s) Used to Identify Potential Cases	Biologically Plausible Time Window, days
Anaphylaxis	977.8, 977.9, 979.6–979.9, 995.0–995.4, 999.4, 708.0, 708.9, and E949.0–E949.9	0–2
Autoimmune hepatitis	570, 571.4, 573.3, and 573.9	0–60
Bell's palsy	351	0–60
Convulsion	345, 779.0, 779.1, and 780.3	0–14
Demyelinating disease	323.81, 340, 341.1, 341.9, 341.2, and 377.3	0–42
Encephalitis and encephalomyelitis	323.5, 323.8, and 323.9	0–42
Guillain-Barré syndrome	357.0, 357.6, 357.8, 357.9, and 344	0–42
Immune thrombocytopenic purpura	279.12, 287.3–287.5, and 776.1	0–42
Vasculitis	273.2, 287.0, 362.18, 437.4, 443.1, 437.4, 446, 447.6, and 448.9	0–42

Abbreviation: ICD-9, *International Classification of Diseases, Ninth Revision*.

Appendix Table 2. *Source of Case Definition Used for Adverse Events of Special Interest Among Vaccinees Aged ≥65 Years, Lombardy, Italy, 2006–2009*

Outcome (Reference No.)	Source of Case Definition
Guillain-Barré syndrome and Miller Fisher syndrome (12), Bell's palsy (13), encephalitis (14), convulsion (15), anaphylaxis (16), immune thrombocytopenia (17)	Brighton Collaboration
Acute transverse myelitis (18)	Transverse Myelitis Consortium Working Group (2002)
Optic neuritis (19)	Guidelines in the published literature
Multiple sclerosis (20)	Revised McDonald criteria
Vasculitis (21)	American College of Rheumatology
Autoimmune hepatitis (22)	International Autoimmune Hepatitis Group