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Evidence of increased clinical protection of an MF59-adjuvant influenza vaccine compared to a non-adjuvant vaccine among elderly residents of long-term care facilities in Italy

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SUMMARY

We evaluated whether the increased immunogenicity provided by an MF59-adjuvant influenza vaccine translates into increased protection among the elderly. Residents of 25 long-term care facilities received either the adjuvant or a non-adjuvant vaccine. The odds ratios (OR) of influenza-like illness were calculated for non-adjuvant *vs.* adjuvant vaccine recipients, also stratifying for chronic cardiovascular, respiratory, and renal diseases. The risk was higher for the non-adjuvant vaccine recipients and highest for those with respiratory disease (OR 2·27, 95% CI 1·09–4·82) and cardiovascular disease (OR 1·88; 95% CI 1·31–2·72). In this study the MF59-adjuvant vaccine provided superior clinical protection among the elderly, especially those with chronic diseases.

INTRODUCTION

Influenza continues to be a major public-health problem, with epidemics leading to significant increases in morbidity and mortality, in addition to the burden in terms of health costs [1]. Influenza is most severe among persons with a weakened immune system, including the elderly and those with chronic diseases. In fact, because they are at a high risk of serious complications of influenza, such as exacerbation of chronic heart, kidney, and respiratory conditions, and are subject to age-related decline in T-cell function, the elderly are considered as one of the primary target groups for influenza vaccination [2]. However, although the efficacy of traditional vaccines has been demonstrated in preventing influenza and its complications among immunocompetent adults [3, 4], these vaccines are somewhat less efficacious among the elderly [5–10].

Attempts to create more efficacious vaccines have included the use of adjuvants for increasing immunogenicity. For example, when compared to non-adjuvant vaccines, an influenza vaccine composed of subunit influenza antigens and combined with a proprietary oil-in-water MF59-adjuvant emulsion [11] has been shown to be associated with increased immunogenicity among the elderly, especially those with chronic conditions [12–15]. Nonetheless, it remains to be determined whether or not this vaccine actually provides increased protection against influenza and its complications.

For a brief period after the licensing of the MF59-adjuvant vaccine in 1997, the public long-term care facilities in two provinces in Italy used both this vaccine and a conventional non-adjuvant vaccine, with the choice being left to the individual facility. In light of reports of the increased immunogenicity provided

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by the adjuvant vaccine, we conducted a study in these facilities in order to compare the two vaccines in terms of actual clinical protection among the elderly in general and among those with chronic underlying diseases, with the ultimate goal of having all of the facilities opt for purchasing the superior vaccine. The results of this investigation are presented herein.

METHODS

The patients involved in this study were residing in December 1998 in the 25 public long-term care facilities in the Provinces of Udine (population of approximately 520 000) and Pordenone (population of approximately 290 000), which are located in the region of Friuli-Venezia Giulia (northern Italy, one of Italy's 20 regions) [17]. The period of observation of the study was from 30 November 1998 to 29 March 1999.

For each resident, the treating physician used a standardized form to collect data on influenza; the physician was not aware of the specific vaccine used. Vaccination had been performed before the influenza season, in October and November, 1998.

The residents had received either adjuvant Fluad® vaccine (Chiron Vaccines, Siena, Italy) or the non-adjuvant subunit vaccine Agrippal S1® (Chiron Vaccines), which was registered in 1986 and has since been used in Italy, along with other conventional vaccines. Both vaccines were administered as a single dose injected in the deltoid muscle. Each dose of the two vaccines contained 15 g of the influenza strains A/Sydney/5/97-like (H3N2), A/Beijing/262/95-like (H1N1), and B/Beijing/184/93. The choice of the vaccine was left to the discretion of the specific facility and was generally made on the basis of product availability; none of the facilities used both vaccines.

Once a week during the observation period, the treating physician collected data on the occurrence of influenza-like illness, diagnosed as a sudden onset of acute respiratory affection, with axillary fever $\geqslant 38\ ^{\circ}C$, at least one general symptom [i.e. headache, general malaise, feeling feverish (sweating and chills), and/or asthenia]; and at least one respiratory symptom (i.e. cough, sore throat, and/or nasal congestion).

At the time of vaccination, the treating physician also collected data on the presence of chronic heart, respiratory, and renal disease, which was determined based on whether or not the resident had been hospitalized in the past for these conditions (which can be traced back as far as 25 years) or was currently being treated for them. Based on the presence of the underlying diseases, the residents were categorized into five groups: those with none of these diseases; those with heart disease alone; those with respiratory disease alone; those with renal disease alone; and those with more than one of these diseases. Vaccination was offered to all residents, independently of the presence of these conditions.

The personal data on residents were provided by the local Registrar's Office and by the care facilities. All data were sent to the local departments of Public Health, which forwarded the data to the study's Coordinating Centre in Gemona, where data analysis was performed using Epi-Info software, version 3.3 (CDC, Atlanta, GA, USA).

Statistical analysis

The risk of developing influenza-like illness was calculated for the non-vaccinated residents compared to the vaccinated residents and for the group vaccinated with the non-adjuvant vaccine compared to those vaccinated with the MF59-adjuvant vaccine; considering, for the latter analysis, only those facilities that both reported influenza-like illness and provided information on the presence of underlying chronic disease ($n=15$). We also calculated the odds ratios (OR) of developing influenza-like illness for the non-adjuvant vaccine recipients *vs.* the MF59-adjuvant vaccine recipients for each of the five chronic disease groups. Vaccine effectiveness was calculated using the equation $1-\mathrm{OR}$, which allowed the impact of vaccination on the population to be estimated.

RESULTS

The study population consisted of 3173 persons (645 men and 2528 women) residing in the 25 public long-term care facilities in the provinces of Udine and Pordenone. The residents ranged in age from 23 to 100 years, with a mean age of 85 (± 10) years. Non-elderly persons (i.e. <65 years of age) represented 3·65% of the study population.

Overall, 2965 (93·44%) of the residents had been vaccinated (1478 with the non-adjuvant vaccine and 1487 with the MF59-adjuvant vaccine). The remaining residents were not vaccinated because they refused. In nearly all of the facilities, vaccination had been performed for more than 90% of the residents.

The number and percentage of cases of influenza-like illness among the vaccinated and non-vaccinated residents, and the type of vaccine received, by facility,

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Table 1. *Number and percentage of cases of influenza-like illness among vaccinated and non-vaccinated residents of 25 long-term care facilities in the provinces of Udine and Pordenone, Italy, 1998–1999*

Location of facility	No. of residents	Number (%) of influenza-like illness cases among vaccinated persons	Number (%) of influenza-like illness cases among non-vaccinated persons	Vaccine used: MF59-adjuvant or non-adjuvant
Aviano	81	49/80 (61·3%)	1/1 (100%)	MF59-adjuvant
Cividale	250	64/241 (26·6%)	9/9 (100%)	Non-adjuvant
Codroipo	130	14/121 (11·6%)	1/9 (11·1%)	Non-adjuvant
Cordenons	107	0/107	0/0	MF59-adjuvant
Gemona	59	0/59	0/0	Non-adjuvant
Gemona (Convento)	70	1/58 (1·7%)	0/12	Non-adjuvant
Gemona (Sereni Orizzonti)	15	5/15 (33·3%)	0/0	Non-adjuvant
Latisana	59	11/59 (18·6%)	0/0	MF59-adjuvant
Maniago	84	34/75 (45·3%)	6/9 (66·7%)	MF59-adjuvant
Moggio	56	0/56	0/0	Non-adjuvant
Morsano	128	0/128	0/0	MF59-adjuvant
Paluzza	113	2/105 (1·9%)	0/8	Non-adjuvant
Pordenone (Casa Serena)	232	29/231 (12·5%)	0/1	MF59-adjuvant
Pordenone (Umberto I)	104	9/104 (8·6%)	0/0	MF59-adjuvant
Sacile	91	22/90 (24·4%)	1/1 (100%)	MF59-adjuvant
San Giorgio	130	44/129 (34·1%)	0/1	Non-adjuvant
San Vito	240	17/238 (7·1%)	1/2 (50·0%)	MF59-adjuvant
Sequals	73	17/72 (23·6%)	0/1	MF59-adjuvant
Spilimbergo	215	2/215 (0·9%)	0/0	MF59-adjuvant
Tarcento	203	23/186 (12·4%)	1/17 (5·9%)	Non-adjuvant
Tolmezzo	146	27/133 (20·3%)	0/13	Non-adjuvant
Tricesimo	98	34/86 (39·5%)	4/12 (33·3%)	Non-adjuvant
Udine (city)	382	96/272 (35·3%)	38/110 (34·5%)	Non-adjuvant
Venzone	18	0/18	0/0	Non-adjuvant
Zoppola	89	0/88	1/1 (100%)	MF59-adjuvant

Odds ratio for developing influenza-like illness (non-vaccinated *vs.* vaccinated): 2·16 (95% CI 1·56–2·98).

are shown in Table 1. Influenza-like illness was diagnosed in 30·4% of the residents who had not been vaccinated and in 16·9% of those who had been vaccinated, for an overall vaccination effectiveness of 54% (OR 2·16, 95% CI 1·56–2·98). The estimated effectiveness was 94·0% (47–100%) for the MF59-adjuvant vaccine and 24·5% (0–45%) for the conventional vaccine.

Five facilities reported no cases of influenza-like illness. These facilities and another five facilities that did not provide information on underlying chronic diseases were excluded from the analysis for comparing the effectiveness of the two vaccines.

For the 15 facilities that both reported influenza-like illness and provided information on the presence of underlying chronic diseases, Table 2 illustrates the number of influenza-like illness cases among all residents ($n=2278$) and those who had been vaccinated ($n=2094$), by type of vaccine and facility. Of the 1168 residents vaccinated with the non-adjuvant vaccine, 302 (25·9%) developed influenza-like illness, compared to 174 (18·8%) of the 926 residents vaccinated with the MF59-adjuvant vaccine (OR 1·52, 95% CI 1·22–1·88). In terms of effectiveness, the MF59-adjuvant vaccine was superior to the conventional vaccine (80·1% *vs.* 57·1%). When also considering the five facilities where no cases were diagnosed, the OR of developing influenza-like illness for non-adjuvant *vs.* MF59-adjuvant vaccine recipients was 1·72 (95% CI 1·39–2·12). When considering all 25 facilities (i.e. including the five that did not provide information on chronic diseases), the OR was 1·80 (95% CI 1·47–2·21).

When stratifying for the presence of chronic underlying diseases, the OR of developing influenza-like illness for non-adjuvant vaccine recipients ($n=1168$) *vs.* the MF59-adjuvant vaccine recipients ($n=926$) was highest for persons with respiratory disease (OR 2·27, 95% CI 1·09–4·82), followed by those with heart disease (OR 1·88, 95% CI 1·31–2·72).

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Table 2. *Number of residents, vaccinated residents, residents with influenza-like illness and vaccinated residents with influenza-like illness for the 15 facilities in which influenza-like illness was diagnosed and which also provided information on underlying chronic diseases, by type of vaccine and facility; provinces of Udine and Pordenone, Italy, 1998–1999*

Location of nursing home	Total no. of residents	Number (%) of vaccinated residents	Total no. of residents with influenza-like illness	No. of vaccinated residents with influenza-like illness
Non-adjuvant vaccine				
Cividale	250	241 (96·4%)	73	64
Codroipo	130	121 (93·1%)	15	14
San Giorgio	130	129 (99·2%)	44	44
Tarcento	203	186 (91·6%)	24	23
Tolmezzo	146	133 (91·1%)	27	27
Tricesimo	98	86 (87·8%)	38	34
Udine (city)	382	272 (71·2%)	134	96
Total	1339	1168 (87·2%)	355	302
%		87·2		25·9
MF59-adjuvant vaccine				
Aviano	81	80 (98·8%)	50	49
Latisana	59	59 (100)	11	11
Maniago	84	75 (89·3%)	40	34
Pordenone (Casa Serena)	232	231 (99·6%)	29	29
Pordenone (Umberto I)	104	104 (100)	9	9
Sacile	91	90 (98·9%)	23	23
Sequals	73	72 (98·6%)	17	17
Spilimbergo	215	215 (100)	2	2
Total	939	926 (98·6%)	181	174
%		98·6		18·8

Odds ratio for developing influenza-like illness (non-adjuvant vaccine recipients *vs.* MF59-adjuvant vaccine recipients): 1·52 (95% CI 1·22–1·88).

DISCUSSION

Before discussing the results of this study, some very obvious limitations need to be addressed. First of all, the efficacy of a vaccine is best evaluated through randomized clinical trials, which allow major biases to be avoided, for example, differences in study populations and in attack rates. This requires sophisticated statistical procedures. In our study, no randomization was performed (the 25 centres were free to choose the specific vaccine), which could naturally lead to a number of biases.

This said, we believe that the results of this study are nonetheless intriguing. To the best of our knowledge, this is the first direct comparison between an adjuvant and a non-adjuvant influenza vaccine with respect to clinical outcome, and it offers some evidence that the MF59-adjuvant vaccine, compared to a conventional non-adjuvant vaccine, may provide increased clinical protection among elderly persons in long-term care facilities. This finding is consistent with the increased immunogenicity of this vaccine and with the direct correlation between immunogenicity and the actual level of protection reported by large field trials and viral challenge experiments [18–25]. Our findings also suggest that the beneficial effects of the MF59-adjuvant vaccine may be even greater for elderly persons with underlying chronic diseases, as deduced from the finding that the OR of developing influenza-like illness was higher for those persons with respiratory or heart disease, compared to the OR calculated when not stratifying for underlying chronic diseases. This is consistent with previous studies showing that the MF59-adjuvant vaccine is even more immunogenic in elderly persons with underlying chronic diseases [15] and those with low pre-immunization haemagglutination inhibition influenza virus antibody titres [12]. With regard to clinical outcomes, a recent case-control study performed in Spain reported that an MF59-adjuvant influenza vaccine

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had an effectiveness of 48% in reducing hospital admissions for pneumonia in a community-dwelling elderly population when comparing vaccinated to non-vaccinated individuals [26]. In our study, it was unfortunately not possible to estimate the risk of developing complications among persons with chronic underlying diseases who developed influenza-like illness. In fact, complications of influenza-like illness are generally difficult to diagnose in this setting, which was one of the reasons for which a standard definition of influenza-like illness was chosen [16].

With regard to the specific choice of statistical methods in our study, although the analysis simply consisted of calculating the ORs of developing influenza-like illness, comparing the two vaccines, it must be stressed that the study was conducted for decision-making purposes (i.e. in order to eventually decide if all of the facilities should use the superior vaccine). For this reason, the analysis had to be robust, and for practical reasons, such as difficulties in diagnosing complications of influenza-like illness in this setting [16], it was performed using an end-point that can be evaluated with relative ease yet which can be considered as a marker of more serious related events [16, 27]. In fact, based on the results of this analysis, the MF59-adjuvant vaccine is now the only influenza vaccine used in the public long-term care facilities of the two provinces. Moreover, the decision to calculate the ORs only for those facilities in which cases of influenza-like illness were diagnosed was based on the assumption that the absence of cases signified that the virus had not been introduced in the facility. However, in doing so, we excluded those facilities in which the vaccines may have been 100% effective and thus, we may have underestimated the effectiveness of the vaccines. In order to avoid biases, we could have also excluded the Udine nursing home as it showed the highest attack rates of all facilities but even then the superiority of the adjuvant vaccine over the subunit remains statistically unchanged. High attack rates have also been observed in other homes such as Cividale, Tarcento, Tricesimo and San Giorgio. These data might be explained by the lower beneficial effects in terms of increased clinical protection of the subunit vaccine in this particular at-risk population and confirms the data coming from Tolmezzo whereby a high percentage of subjects receiving the non-adjuvant vaccine experienced influenza-like illness whereas no cases were reported among the non-vaccinated group. In Spilimbergo very few cases occurred among those receiving the adjuvant vaccine, evidence that this vaccine, compared to a conventional non-adjuvant vaccine, may provide increased clinical protection.

The efficacy of a vaccine obviously depends on whether or not it antigenically matches the strains circulating in the community [8]. During the 1998–1999 influenza season in Italy, A/H1N1 and A/H3N2, both of which were contained in the two vaccines tested, were circulating, and the A/H3N2 strain was responsible for severe regional and national level epidemics of 'Australian flu' [28]. Moreover, both A/H1N1 and A/H3N2 represented newly introduced strains, which have a greater impact on public health compared to strains that have already circulated, while A/H3H2, which in the past 10 years has been the most common predominant influenza subtype worldwide, is generally more aggressive in elderly persons [29]. The immune response to A/H3N2 and new strains has been shown to be particularly enhanced by MF59-adjuvant vaccine, compared to conventional products [12, 13]. With regard to the occurrence of influenza-like illness in the care facilities, the observed trend is consistent with that in different areas of Italy during the 1998–1999 influenza season (no national level data are available for that period). Specifically, the season was particularly long (i.e. from January to March), with an epidemic peak occurring during weeks 6–7 of 1999, as observed in the care facilities [28].

In Italy the beneficial effects of the adjuvant vaccine are widely accepted especially in the at-risk elderly suffering from chronic diseases. The fact that the majority of subjects who were offered the MF59-adjuvant vaccine accepted the vaccination could cause a selection bias. However, from a general point of view this kind of selection in such an at-risk type of population can even, to a certain extent, negatively influence the beneficial effects of the adjuvant vaccine.

In addition to the potential biases described above, several specific limitations should be mentioned. In particular, the exclusion of the five facilities that did not provide information on chronic underlying diseases from the comparison of the two vaccines could have affected the results. The participating care facilities also included non-elderly residents, yet these persons only represented 3·65% of the total study population; thus, their inclusion probably did not have a significant impact on the results. Furthermore, we did not take into account the presence of neoplastic diseases for which immunosuppressive therapy could alter the efficacy of the vaccines [30]. We also cannot exclude the possibility that the two vaccine

groups were not homogeneous in terms of their health status, although in order to be admitted to these facilities candidates must first undergo an evaluation that attests to their being non-autonomous. With regard to the question of whether or not the residents of public facilities can be considered as representative of the entire population of long-term facility residents – there are very few private facilities in the two provinces and those operating work in close collaboration with the public health system.

Despite these limitations, the results of this study suggest that the MF59-adjuvant vaccine should be more thoroughly evaluated in terms of its ability to meet the need for an efficacious influenza vaccine among elderly persons in general and those with underlying chronic diseases. The safety and immunogenicity of this vaccine have been extensively evaluated in the elderly, both in the community and in long-term care facilities, and although the vaccine has been shown to be somewhat more reactogenic than conventional vaccines, it is generally well tolerated, with mild and short-lasting adverse reactions [12].

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