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Vaccine 31 (2013) 6122–6128

Contents lists available at ScienceDirect

Vaccine

journal homepage: www.elsevier.com/locate/vaccine

The comparative effectiveness of adjuvanted and unadjuvanted trivalent inactivated influenza vaccine (TIV) in the elderly☆

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ARTICLE INFO

Article history:
Received 30 January 2013
Received in revised form 16 June 2013
Accepted 25 July 2013
Available online 6 August 2013

Keywords:
Influenza
Vaccine
Effectiveness
Adjuvant
Elderly

ABSTRACT

Background: Influenza is associated with a high mortality and morbidity in older adults. Vaccination remains the most effective method of preventing influenza and its consequences, however, vaccine effectiveness decreases with increasing age and increasing immunosenescence. In older adults, immunogenicity studies suggest an MF59 adjuvanted influenza vaccine (ATIV, Fluad®) may help.
Methods: We evaluated the comparative effectiveness of ATIV, and unadjuvanted trivalent influenza vaccine (TIV) in reducing laboratory confirmed influenza in the elderly. Elderly in three health authorities during winter 2011–12 were included in a community based case control study design. Cases tested positive and controls tested negative for influenza. Subjects with known immunosuppression were excluded. Logistic regression was used to calculate the odds ratio of vaccination (vs. no vaccination) in cases and controls. ATIV and TIV effectiveness was described.
Results: A total of 282 eligible participants were enrolled (84 cases). Almost half (136) were in a long term care facility and were 85 years of age or older (132) vaccine effectiveness decreased with increasing age. In a variety of multivariate analyses, ATIV was significantly protective at around 60% ($p = 0.02$), with only residence in long term care and health authority also significant. Vaccine effectiveness increased in non-long term care residents. In multivariate analyses TIV was ineffective.
Conclusion: An MF59 adjuvanted vaccine provided significantly improved protection against influenza in the elderly.

1. Introduction

Influenza is associated with substantial morbidity and mortality especially in older adults. Each year an average of 20,000 hospitalizations and between 2000 and 8000 deaths are attributed to influenza and pneumonia in Canada, the eighth leading cause of death [1,2]. Increasing age, particularly over 70 years, brings further increases in the risk of all-cause mortality or hospitalization with influenza or pneumonia [3]. In addition to causing deaths from acute influenza illness and secondary bacterial pneumonia, influenza has been associated with increased mortality from ischaemic heart disease, cerebrovascular disease, and diabetes [4]. Up to 90% of influenza-related deaths occur in persons aged 65 years or older [2].

Vaccination remains the most effective method of preventing influenza virus infection and its sequellae [5]. However, vaccine effectiveness may be only 60% in healthy adult groups [6] and effectiveness decreases with increasing age and increasing immunosenecence. In older adults, seasons with significant vaccine/virus mismatch have been associated with decreased antibody response [7] and lack of vaccine effectiveness [8]. Enhanced vaccines are hence needed to provide adequate protection in the elderly, particularly in mis-matched years.

A number of immunogenicity studies have shown superiority of ATIV, a two-component vaccine consisting of three influenza immunizing antigens, with an MF59 oil in water adjuvant (ATIV),

DOIs of original articles: http://dx.doi.org/10.1016/j.vaccine.2013.12.032, http://dx.doi.org/10.1016/j.vaccine.2015.01.045

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http://dx.doi.org/10.1016/j.vaccine.2013.07.059

against unadjuvanted split virus and subunit trivalent influenza vaccines (TIV) [9]. While these have varied in the extent (and presence) of superiority in different studies and against different influenza strains, the overall picture has been for improved immunogenicity.

The aim of this study was to evaluate, using a prospective community based case–control design in the elderly, the relative vaccine effectiveness against microbiologically confirmed influenza illness of ATIV and TIV, in comparison to no vaccination.

2. Methods

In British Columbia all elderly over the age of 65 years are entitled to free influenza vaccine. In the 2011–12 season a combination of standard TIV and adjuvanted vaccines licensed in Canada for use in the elderly were available. All vaccines contained the recommended strains for the Northern Hemisphere that year, antigens from an A/California/7/2009 (H1N1)-like virus, an A/Perth/16/2009 (H3N2)-like virus and a B/Brisbane/60/2008-like virus.

In two health authorities, Fraser Health Authority (FHA) and Vancouver Coastal Health Authority (VCH), elderly residents over 75 years and all those in long term care facilities were preferentially given Fluad® a trivalent, surface antigen, inactivated influenza virus vaccine, adjuvanted with MF59C.1. The MF59C.1 adjuvant contained in ATIV is an oil-in-water emulsion composed of squalene as the oil phase, stabilized with the surfactants polysorbate80 and sorbitantrioleate, in citrate. On Vancouver Island (VIHA) residents in long term care were offered ATIV, but all other elderly were offered standard TIV predominantly Fluviral® (GSK), a trivalent split virion influenza vaccine.

The decision about which vaccine to use was made by the health authorities independent of the discussions to study the impact of these decisions. Due to shortages of certain vaccine brands at some stages, some people aged 65–75 years in FHA and VCH were vaccinated with ATIV although the initial study design excluded this age group.

Apart from two hospital sites, all influenza tests in the three health authorities are transferred to a central provincial laboratory. Primary care practitioners in the three health authorities were sent flocked Dacron swabs before the start of the influenza season and asked to take nasopharyngeal swabs from those with influenza like illness (ILI), inoculate them in viral transport media (VTM) and transport them to the central laboratory.

Testing of individuals was performed as part of routine clinical care. Testing was performed at the BCCDC Public Health Microbiology and Reference Laboratory located at the BC Centre for Disease Control using a validated fourplex PCR assay for the detection of Influenza A and B and respiratory syncytial virus based on the methods of Chen et al. [10]. The assay simultaneously targets the Influenza A, M gene, the Influenza B, NP gene and the Respiratory Syncytial Virus, L gene as well as RnaseP which is a housekeeping gene to ensure sample, extraction and amplification integrity. Nasopharyngeal swabs were collected from patients and placed in viral transport media. After vortexing, 200 μl of sample was extracted using a MagMAX™ Express-96 Deep Well Magnetic Particle Processor (Applied Biosystems®, Canada) yielding an elution volume of 60 μl. Nucleic amplification was performed on an Applied Biosystems 7500 Fast Real-Time PCR System (Applied Biosystems®, Canada) using 5 μl of eluate. The lower limit of detection for each of the three viruses is between 10 and 100 copies. Influenza A reactive specimens were also typed using type specific primers targeting the HA gene as per Chen et al. and/or underwent HA gene sequencing.

The study received ethics approval from the Research Ethics committees of Vancouver Coastal and Fraser Health Authorities and the University of British Columbia Ethics Committee. The study was registered with ClinicalTrials.gov (NCT01424371).

Commencing on December 12th, the first day when more than one positive sample in a week occurred, we selected all adults over 65 years of age who were tested for influenza. The study continued until April 2nd, which represented the last positive influenza case of the season for the study population.

Participants were included if they were 65 or older as of the influenza test date, had influenza like symptoms (ILI) and were swabbed and tested for influenza, and had no immunodeficiency conditions. Additionally, patients tested more than seven days after commencement of ILI were excluded.

Participants were classified as cases if the respiratory sample was influenza positive. They were classified as a control if the test was negative and they met a clinical case definition of influenza-like-illness. Information on age, sex, hospitalization, residence in a long term care facility, immune-suppression, and coexisting medical conditions was collected by direct telephone interview with the study participant or their caregiver. We also confirmed the diagnosis of an influenza-like-illness through self-report or review of long term care records. The vaccination status and date and type of vaccination were confirmed through the records of the healthcare practitioner. Interviewers were not blinded to the status of cases or controls. The same central interviewers were used in all three health authorities.

Study participants were classified as vaccinated if they had received a dose of the influenza vaccine at least 14 days before the onset of symptoms and as 'not vaccinated', if they received no vaccination or received the first dose within 14 days of onset of symptoms.

Data were entered and analyzed using SPSS for Windows, version 17.0. A statistical significance level of 0.05 was adopted. Testing by the Chi-square analysis, Fishers exact test or *t*-tests was used to assess the significant differences in characteristics between cases and controls, and between vaccinated and unvaccinated individuals. Odds ratios were calculated using laboratory confirmed influenza as the primary outcome and vaccination status as the primary exposure. VE was calculated as one minus the odds ratio based on the formula by Greenwood and Yule [11].

The primary outcome of interest was testing positive for influenza. The independent factors assessed included sex, vaccine type (ATIV or TIV), age group, long term care residency (LTCF), and the presence of chronic disease. Participants who reported a date and brand of influenza vaccine were recorded as vaccinated, and those reporting not being vaccinated were recorded as such. Thus influenza vaccination was treated as a dichotomous variable, and any cases or controls that reported an unknown vaccination status were excluded. Age, determined at the time of testing, was categorized into <75, 75–84, and 85 years in addition to being treated as a continuous variable. Chronic disease was based on one or more of self-reported chronic cardiac, respiratory or neurological conditions. Sex and long-term care residency at the time of testing were also treated as dichotomous variables. Information on week of testing and health authority residence was used to control for influenza exposure.

To estimate the association between potential dependent (i.e. predictor) variables and the outcome (i.e. testing positive for influenza) we used logistic regression models. All univariate variables with a $p < 0.25$, deemed to be potential confounders, or thought to be a potentially useful predictors were included in the multivariate model. Variables, which provided little predictive power, were excluded. Variables were assessed for multicollinearity, effect modifiers and confounders.

Subgroup analyses were conducted into more homogenous strata that might reduce the effect of residual confounders or bias and to explore vaccine effectiveness (VE). Subgroups included

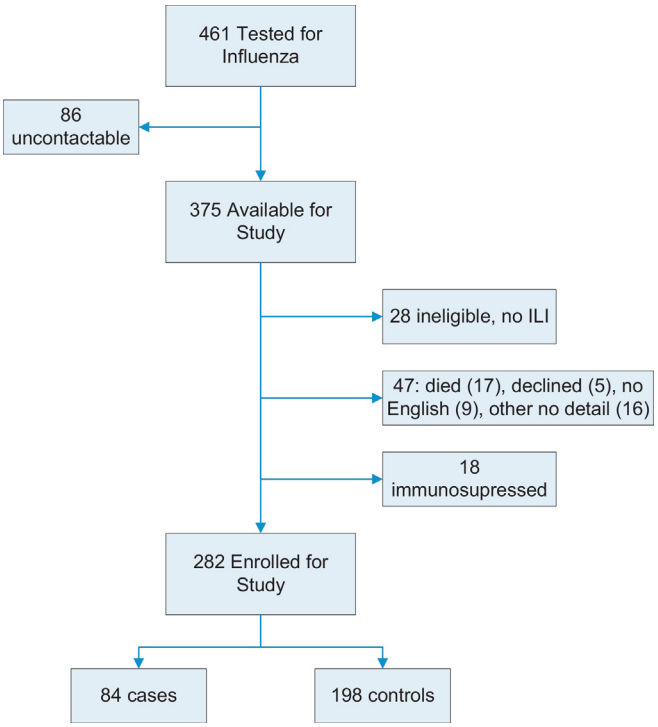

Fig. 1. Characteristics of study selection.

long-term and non-long-term care residents. In order to perform a direct comparison between TIV and ATIV, a relative vaccine effectiveness analysis was performed on only those study participants vaccinated.

3. Results

3.1. Participants

The review period commenced on December 12th 2011, the first date on which more than one positive case in a week occurred. A total of 461 influenza tests were performed from then until April 2nd when cases ceased. Of these, 17 cases were deceased and another 86 cases were unable to be contacted leaving 358 available for recruitment. Of those contactable, 28 were ineligible as they had no ILI, 18 were ineligible as they were immune-suppressed, 25 had insufficient English or incomplete information and 5 more declined to participate, leaving a total of 282 available participants (79%) enrolled in the study, 84 cases and 198 controls (see Fig. 1).

Influenza cases were not uniformly distributed over time through the health authorities. The influenza epidemic curve for the season in the three health authorities is shown in Fig. 2 (including cases not in the target range) and the distribution over time of cases and controls in the study shown in Fig. 3.

Participants' demographic characteristics are presented in Table 1. The mean age of the sample was 83.0 years (standard error, 0.51) and almost one half were 85 years or older. The majority of participants were females (186, 66%), residents of long term care facilities (160, 57%), and reported at least one chronic disease (250, 89%). The most commonly reported chronic disease categories were cardiac (203, 72%) followed by neurological (110, 39%) and respiratory condition (85, 30%). One third of cases (30%) were hospitalized for their ILI symptoms. A total of 227 (81%) subjects were vaccinated against the influenza, and among those vaccinated, 73% were vaccinated with ATIV compared to 27% who were vaccinated with TIV. Influenza subtyping was done for the 84 cases, of which

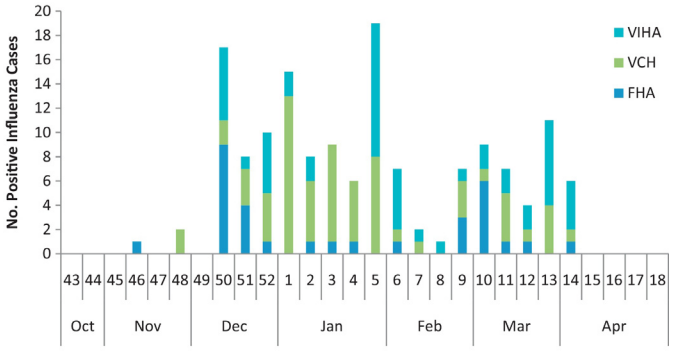

Fig. 2. Influenza epidemic curve for the three participating health authorities for the 2011/12 influenza season ($n = 153$). *Based on date of sample collection.
Source: Public Health Microbiology & Reference Laboratory. BC CDC.

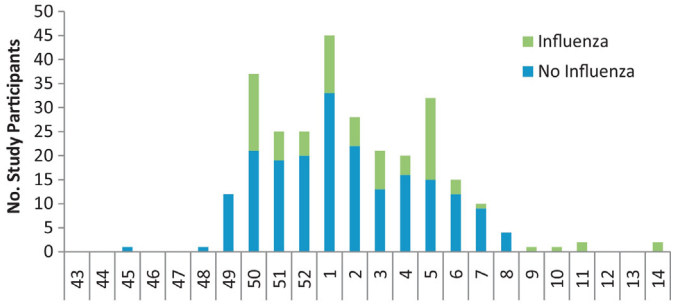

Fig. 3. Count of study participants, by status and onset of symptoms ($n = 282$). *Epi week assigned based on onset of symptoms, not date of sample collection.

Table 1
Characteristics of study population.

	ATIV ($n = 165$)		TIV ($n = 62$)		Unvaccinated ($n = 55$)	
Health authority						
Fraser	78	47.3	9	14.5	17	30.9
Vancouver coastal	69	41.8	16	25.8	21	38.2
Vancouver island	18	10.9	37	59.7	17	30.9
Long term care facility						
Yes	127	77.0	18	29.0	15	27.3
No	38	23.0	44	71.0	40	72.7
Gender						
Males	46	27.9	24	38.7	29	52.7
Females	119	72.1	38	61.3	26	47.3
Age groups						
<75	13	7.9	22	35.5	17	30.9
75–84	56	33.9	23	37.1	19	34.5
85+	96	58.2	17	27.4	19	34.5
Chronic disease						
Yes	145	87.9	58	93.5	47	85.5
No	20	12.1	4	6.5	8	14.5
Respiratory chronic condition						
Yes	46	27.9	21	33.9	18	32.7
No	119	72.1	41	66.1	37	67.3
Cardiac chronic condition						
Yes	118	71.5	49	79.0	36	65.5
No	47	28.5	13	21.0	19	34.5
Neurological chronic condition						
Yes	83	50.3	14	22.6	13	23.6
No	82	49.7	48	77.4	42	76.4
Hospitalized						
Yes	27	16.4	31	50.0	25	45.5
No	138	83.6	31	50.0	30	54.5
Influenza						
Yes	42	25.5	23	37.1	19	34.5
No	123	74.5	39	62.9	36	65.5

Table 2
Study population descriptives for cases and controls.

	Case ($n=84$)		Control ($n=198$)		Total ($n=282$)		p-Value
	n	%	n	%	n	%	
Health authority							
Fraser	15	17.9	89	44.9	104	36.9[a]	0.000
Vancouver coastal	38	45.2	68	34.3	106	37.6	
Vancouver island	31	36.9	41	20.7	72	25.5	
Long term care facility							
Yes	54	64.3	106	53.5	160	56.7	0.096
No	30	35.7	92	46.5	122	43.3	
Gender							
Males	31	36.9	65	32.8	96	34.0	0.509
Females	53	63.1	133	67.2	186	66.0	
Age groups							
<75	11	13.1	41	20.7	52	18.4	0.066
75–84	25	29.8	73	36.9	98	34.8	
85+	48	57.1	84	42.4	132	46.8	
Chronic disease							
Yes	71	84.5	179	90.4	250	88.7	0.155
No	13	15.5	19	9.6	32	11.3	
Respiratory chronic condition							
Yes	26	31.0	59	29.8	85	30.1	0.847
No	58	69.0	139	70.2	197	69.9	
Cardiac chronic condition							
Yes	58	69.0	145	73.2	203	72.0	0.474
No	26	31.0	53	26.8	79	28.0	
Neurological chronic condition							
Yes	36	42.9	74	37.4	110	39.0	0.388
No	48	57.1	124	62.6	172	61.0	
Hospitalized							
Yes	23	27.4	60	30.3	83	29.4	0.622
No	61	72.6	138	69.7	199	70.6	
Vaccinated							
Yes	65	77.4	162	81.8	227	80.5	0.390
No	19	22.6	36	18.2	55	19.5	
Vaccine type							
ATIV	42	50.0	123	62.1	165	58.5	0.160
TIV	23	27.4	39	19.7	62	22.0	
Unvaccinated	19	22.6	36	18.2	55	19.5	

[a] p-Value < 0.05, based on a Chi-squared test.

12 (14%) were influenza B, 1 (1%) was H1N1 and 71 (85%) were H3N2.

T-test and Chi-squared analyses indicated that the cases and controls differed significantly only in their age and their health authority ($\chi^2_{(2,282)}$ 19.66, $p<.05$). Compared to the controls, cases were slightly older (84.8 vs. 82.2, $p=0.018$). A larger percentage of cases were Vancouver Coastal and Vancouver Island, while a large percentage of controls were from Fraser. No other differences were found among cases and controls (Table 2). The type specific results were similar for H3N2 and were not possible for the other types due to low numbers.

3.2. Univariate analysis

The vaccine effectiveness of any vaccine was 24% (CI: −42% to 59% NS). The VE of ATIV for the whole population was 35% (CI: −25% to 81% $p=0.2$) and for TIV was −12%.

In the analysis of baseline characteristics tested as potential confounding or risk factors, only age and health authority were significantly related to the outcome variable (Table 3). Compared to participants under 75 years of age, those 85 years of age or older were 2.1 times more likely to have laboratory confirmed influenza.

A subgroup analysis of study participants not in a long-term care facility ($n=122$) showed a significant vaccine effectiveness of 63% ($p=0.023$) for the receipt of any vaccine, with a ATIV vaccine effectiveness of 73% (CI: 14–92% $p=0.03$). The vaccine effectiveness of TIV in this group was 42% but was not significant ($p=0.30$).

3.3. Multivariate analysis

Logistic regression was used to assess the effectiveness of vaccination status while controlling for age, sex, long term care residency, chronic conditions, health authority, and week of testing. The analysis was completed using the total sample with a subgroup analysis completed by long term residency status and by type of influenza. None of the specific chronic conditions or hospitalization significantly contributed to the model and these were thus not included in the final model. While age was not found to be significant in the model, the preferential administration of the vaccine was based on age, and for this reason was included in the model.

We also tested for a possible interaction effect between vaccination and hospitalization, vaccination and long term care residency, long term care residency and age, and vaccination and age. None of the interactions were found to be significantly related to the outcome measure and, therefore, these interaction terms were removed from the final models to retain degrees of freedom. No effect modifiers or multi-collinearity was observed.

Table 4 presents the results for the final multivariate logistic regression model. When controlling for the variables indicated above, ATIV had a vaccine effectiveness of 58% (CI: 5–82, $p<0.04$) and TIV was ineffective. Other significant factors in the model were residence in a long term care facility and health authority. Substituting age as a grouped variable in the model did not alter VE calculations.

Similar results were found among non-long-term care residents. When controlling for age, gender, presence of a chronic condition, health authority, and week of testing those vaccinated with ATIV

Table 3
Univariate logistic regression analysis. Crude odds ratio for contracting the season flu according to binomal logistic regression.

	OD	*L* 95%CI	*H* 95%CI	*p*-Value
Health authority				
Fraser	–			
Vancouver coastal	3.316	1.687	6.518	0.001
Vancouver island	4.486	2.186	9.207	0.000
Long term care facility				
Yes	1.562	0.923	2.645	0.097
Gender				
Males	–			
Females	0.836	0.490	1.424	0.509
Age	1.038	1.006	1.070	0.020
Age groups				
<75	–			
75–84	1.276	0.570	2.857	0.553
85+	2.130	1.002	4.527	0.049
Chronic disease				
Yes	0.580	0.272	1.236	0.158
Respiratory chronic condition				
Yes	1.056	0.607	1.838	0.847
Cardiac chronic condition				
Yes	0.815	0.466	1.427	0.475
Neurological chronic condition				
Yes	1.257	0.748	2.112	0.388
Hospitalized				
Yes	0.867	0.492	1.529	0.623
Vaccinated				
Yes	0.760	0.407	1.422	0.391
Vaccine type				
Unvaccinated	–			
ATIV	0.647	0.335	1.248	0.194
TIV	1.117	0.524	2.384	0.774

were less likely to test positive for influenza compared to those unvaccinated (VE of 72%, 95% CI: 2–93%, *p*-value = 0.047) TIV was ineffective ($p = 0.623$).

Among the vaccinated study population ($n = 227$), the relative VE was 63% (4–86%, $p = 0.04$) when comparing ATIV to TIV directly (see Table 5).

In summary, the VE for ATIV was 58% (5–82%, $p = 0.04$) overall for this study population, and 72% (2–93%, p = 0.047) for non-long term care residents.

Table 4
Multivariate analysis. Adjusted odds ratio for contracting the season flu according to binomal logistic regression.

	OD	*L* 95%CI	*H* 95%CI	*p*-Value
Vaccine				
Unvaccinated	–			
ATIV	0.419	0.185	0.951	0.038
TIV	1.017	0.432	2.392	0.970
Long term care facility				
No	–			
Yes	2.774	1.289	5.970	0.009
Gender				
Males	–			
Females	0.721	0.394	1.320	0.289
Age	1.037	0.996	1.079	0.076
Chronic disease				
No	–			
Yes	0.310	0.128	0.752	0.010
Health authority				
Fraser	–			
Vancouver coastal	4.595	2.181	9.682	0.000
Vancouver island	4.906	2.058	11.700	0.000
Testing week	1.015	0.926	1.114	0.747
Vaccinated[a]				
No	–			
Yes	0.620	0.301	1.274	0.193

[a] Replacing vaccine type in model.

Table 5
Relative vaccine effectiveness multivariate analysis. Adjusted odds ratio for contracting the seasonal flu according to binomal logistic regression among those vaccinated ($n = 227$).

	OD	*L* 95%CI	*H* 95%CI	*p*-Value
Vaccine				
TIV	–			
ATIV	0.37	0.14	0.96	0.040
Gender				
Males	–			
Females	0.61	0.30	1.22	0.159
Age	1.01	0.96	1.06	0.696
Long term care facility				
No	–			
Yes	5.38	2.08	13.93	0.001
Chronic disease				
No	–			
Yes	0.28	0.10	0.82	0.021
Health authority				
FH	–			
VCH	4.92	2.10	11.56	0.000
VIHA	5.55	1.93	16.02	0.002
Week No.	0.95	0.84	1.07	0.396

4. Discussion

In the winter of 2011–12 in British Columbia, an adjuvanted sub-unit trivalent influenza vaccine showed superior vaccine effectiveness against laboratory confirmed influenza than the spilt virion unadjuvanted vaccine.

The overall vaccine effectiveness against the elderly target population was low and TIV was ineffective in all groups except those not in residential care. The superior vaccine effectiveness of the adjuvanted vaccine was seen despite the potential for negative confounding, in which the vaccine was being used more often in those over 85 years of age and in those resident in long term care facilities, settings associated with an increased likelihood of immunosenescence [12–14]. When these factors were taken into account in multivariate models, adjuvanted vaccine had a VE of 58% and TIV was ineffective.

The relative ineffectiveness of TIV in this population was not surprising and had been described before [15,16]. United States surveillance in the study year showed a drift in the circulation of the predominant H3N2 type towards the end of the season and TIV is known to be less effective in these conditions [17]. The improved protection of adjuvanted vaccine across clades was previously seen in studies of H5N1 vaccines [18,19]. Clinical trials have also shown that MF59 adjuvanted vaccines are more immunogenic than conventional nonadjuvanted vaccines and also provide better immunogenicity against drifted seasonal strains that are different from the virus strains included in the vaccine [20].

While this enhanced effectiveness is demonstrated in a single year it is unlikely to be a chance finding. A broad based comparative study in Lombardi over three influenza seasons in Italy found the risk of hospitalization for influenza or pneumonia was 25% lower for adjuvanted vaccine relative to TIV (relative risk = 0.75, CI: 0.57–0.98) [21], and a series of as yet unpublished studies looking at immunogenicity to influenza vaccines in the elderly undertaken at the same time as our study showed an enhanced humoral and cell mediated response to adjuvanted vaccine over both TIV and the intradermal TIV [22].

The study design was based on recruiting all persons over 75 years in the study area. The predominance of persons in long term care and in hospitals and emergency rooms reflected testing in a very low activity influenza season. While all family practitioners were sent swabs and asked to test ILI patients, at no time that winter was there a signal that influenza was circulating, and little testing occurred in the community. It is probable that were more

community dwelling healthy elderly recruited to the study, VE would have been greater for both vaccines, as it was in the subgroup of non-LTCF residents in this study. The significant benefit seen with ATIV over TIV was enhanced by the large number of elderly with co-morbid conditions in the study group, a situation where TIV effectiveness lessens. A randomized controlled trial with an AS03-adjuvanted vaccine in older ambulatory adults, while showing a lesser difference than we found, did have an incremental efficacy of 22% over plain TIV against H3N2 in a post hoc analysis [23].

Our study allocated controls using elderly with ILI who were influenza negative on laboratory testing. This use of a "test negative" design for a community based study of influenza VE was modelled by Orenstein and found to provide a reliable estimate of odds ratio from a case control study when a test with a high specificity is used [24]. The methodology is also consistent with the recommendations of the European CDC for vaccine effectiveness studies [25]. It has previously been used in Canadian settings to assess the pandemic vaccine effectiveness [26].

Vaccine unavailability at times during the vaccination period led to some elderly and in long term care receiving TIV in the 'adjuvanted area'. This did not affect the study outcomes. Similarly, an absence of TIV towards the end of the vaccination period led to some of those under 75 years receiving adjuvanted vaccine. This enabled some assessment of VE in younger groups but the numbers were small. A second year of the study is planned to include a broader age range and an increased focus on community dwelling elderly.

Adjuvanted vaccine is not a panacea in elderly persons with immunosenescence, with a standardized VE in this study of about 60%. However, TIV was ineffective in the same group this year and adjuvanted vaccine appeared to be a significant improvement on the protection available against the known hospitalizations and death in this group.

4.1. Limitations

An observational study design was used. Which vaccine was administered was determined by external factors such as the health authority and the availability of vaccine. However, the evaluation was conducted by the health authorities themselves, and while it would have been unethical to randomize a control group, when public health policy is for all in this age group to be vaccinated, a control group "self-selected" by not being vaccinated. There is a potential for the presence of a healthy vaccine effect, where those that are more health conscious and have a healthier lifestyle are more likely to be vaccinated. However, this bias is minimized in this study population; among elderly, those with chronic conditions and poorer health, are more likely to have their health care provider recommend the vaccine to them. It remains possible though that groups declining vaccination have different thresholds for seeking care and thus being exposed to testing.

The total study subject numbers were very small due to the low level of influenza activity in the community that year. Repeated studies in subsequent years are necessary to confirm findings and look for potential strain variation not assessable due to a relatively homogenous strain year. Similarly, low numbers prevented the evaluation of protection against hospitalization, another important public health outcome.

Blinding of interviewers of the classification of the study participant (i.e. case vs. control) was not possible as the interviews conducted were a little different. However, the key extracted information was the presence and type of vaccination and this is unlikely to have been subject to non-blinding bias by interviewers.

Further limitations of this study were that the analysis did not control for socio-economic status or smoking status other potential confounders. In mitigation, unpublished data from local studies show smoking rates of only 3% in this group, almost certainly due to a mortality factor among smokers in the very elderly.

Acknowledgements

We thank the research nurses involved in the study, Cary Harrison, Lori van der Gugten, and Marilyn Nicholson. We also thank Dr. Meena Dawar of Vancouver Coastal Health Authority for her contributions.

This study was supported by an unrestricted grant-in-aid from Novartis vaccines and by the Fraser Health Authority

Contributions: All authors contributed to the study protocol. P. Van Buynder, S. Konrad and G. Ramler were involved in the analysis of the data. P. Van Buynder, S. Konrad and J. Van Buynder led the writing of the manuscript. J. Van Buynder managed the data collection and study implementation. M. Krajden managed the diagnostic processes and authored this component of the methods. All authors revised the manuscript critically and approved the final version that was submitted.

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