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The confounded effects of age and exposure history in response to influenza vaccination

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ABSTRACT

Numerous studies have explored whether the antibody response to influenza vaccination in elderly adults is as strong as it is in young adults. Results vary, but tend to indicate lower post-vaccination titers (antibody levels) in the elderly, supporting the concept of immunosenescence—the weakening of the immunological response related to age. Because the elderly in such studies typically have been vaccinated against influenza before enrollment, a confounding of effects occurs between age, and previous exposures, as a potential extrinsic reason for immunosenescence.

We conducted a four-year study of serial annual immunizations with inactivated trivalent influenza vaccines in 136 young adults (16 to 39 years) and 122 elderly adults (62 to 92 years). Compared to data sets of previously published studies, which were designed to investigate the effect of age, this detailed longitudinal study with multiple vaccinations allowed us to also study the effect of prior vaccination history on the response to a vaccine.

In response to the first vaccination, young adults produced higher post-vaccination titers, accounting for pre-vaccination titers, than elderly adults. However, upon subsequent vaccinations the difference in response to vaccination between the young and elderly age groups declined rapidly. Although age is an important factor when modeling the outcome of the first vaccination, this term lost its relevance with successive vaccinations. In fact, when we examined the data with the assumption that the elderly group had received (on average) as few as two vaccinations prior to our study, the difference due to age disappeared.

Our analyses therefore show that the initial difference between the two age groups in their response to vaccination may not be uniquely explained by immunosenescence due to ageing of the immune system, but could equally be the result of the different pre-study vaccination and infection histories in the elderly.

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1. Introduction

The World Health Organization and many national health authorities recommend yearly influenza vaccination for people at risk of developing serious complications, including elderly persons over a defined age limit (typically 60 or 65 years). Various studies have described lower serological responses to vaccination in elderly than in young human adults [1–4]. For example, Beyer et al. [5] described how ten studies revealed a better immune response in young subjects than in elderly, 16 could not detect a significant difference, and four found an increased response in the elderly. Another quantitative meta-analysis of 31 studies consistently found lower seroprotection and seroconversion rates in the elderly compared to younger adults [6], findings that are in agreement with results from a database of 48 serological trials performed for regulatory purposes [6,7]. Thus most but not all published studies of serological comparisons report a lower antibody response to influenza vaccination in the elderly than in the young adults. A weakened

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immunological response related to age is known as immunosenescence, and this explanation is commonly used to explain the lower antibody response in elderly cohorts to vaccination.

Here we consider two different mechanistic drivers for immunosenescence. One mechanism concerns intrinsic drivers towards immunosenescence based on the ageing of the immune system, a complex process that is not yet fully understood, and may involve the age-dependent functioning of T-cells and a decreased output of naïve T-cells as a result of involution of the thymus [8–11]. Such an intrinsic immunosenescent process has been observed in studies of influenza-naïve rhesus macaques, where ageing results in declined antibody response to influenza vaccination [12,13].

The effects of such intrinsic immunological drivers may be compounded by extrinsic, or environmental, drivers of immunosenescence. An example of such an environmental contribution towards immunosenescence in reactions to influenza vaccine is previous infection with cytomegalovirus (CMV). CMV antibodies have been reported to increase pro-inflammatory potential, which contributes to unresponsiveness of the immune system. Because the presence of CMV antibody strongly correlates with age, this would also explain lower serological responses to vaccination against influenza in the elderly [14–16]. Similarly, studies on the effect of repeated vaccination in the elderly have proposed the explanation that prior vaccination may attenuate subsequent immune responses upon re-exposure to influenza [17,18].

Because humans partaking in vaccination studies are not naïve to influenza infection and their history of vaccination prior to enrollment is typically unknown, it is difficult to establish the relative contribution and possible interdependence of age and exposure history on immunosenescence. We designed a four-year cohort vaccination study to delineate the intertwined effect of age and repeated exposures on the response to influenza vaccination.

2. Materials and methods

2.1. Subjects and study design

The study was performed from 1996 to 1999 in healthy community-dwelling young and elderly adults living in Hampton Roads, Virginia, United States. The young adults had never received influenza vaccine, and older adults may have been vaccinated previously, but not for at least two years prior to their enrollment in the study. Subjects consented upon enrollment to participation for the duration of the study. The Institutional Review Board of Eastern Virginia Medical School, Norfolk, VA, approved the study protocol and informed consent form. All study participants received an intramuscular injection of the standard dose of trivalent seasonal influenza vaccine (Fluzone®, Sanofi) in each of the study years in which they were enrolled. The health status of all participants of both age groups was very good. All subjects were contacted in the fall of each year to schedule a vaccination visit. Post-vaccination follow-up visits were scheduled in October of each year. Blood samples included 5 cm^3 of serum collected just prior to vaccination, and four weeks post-vaccination.

142 healthy young adults (20–40 years) and 122 healthy older adults (≥65 years) completed the study, *i.e.*, their sequence of vaccinations was uninterrupted during the years, and their pre- and post-vaccination antibody titers were available for all vaccination events and influenza strains involved. The two age groups consisted of four cohorts each, as each year a new cohort of young and elderly adults entered the study. Table 1A shows the numbers of vaccinees per year and cohort. The vaccine strains changed once for each of the three (sub)types in the course of the study, as shown in Table 1B.

Table 1A
Numbers of volunteers, according to age, year of entering the study, and vaccinations within the study. The table also shows the compliance of participants during the study. For example, the cohort of young adults started with 55 young individuals in year 1 (1996), of whom 30 also participated in the second year, 22 in the third year, and 18 in the final year (diagonal).

Age group	Number of vaccinations (NV)	Number of vaccination events				
		1996	1997	1998	1999	All
Young adults	1	55	25	32	24	136
	2		30	14	15	59
	3			22	8	30
	4				18	18
	All	**55**	**55**	**68**	**65**	**243**
Elderly adults	1	33	42	32	15	122
	2		27	38	25	90
	3			24	32	56
	4				21	21
	All	**33**	**69**	**94**	**93**	**289**

Table 1B
Vaccine strain for each year and subtype for both age groups. Vaccine and titration strains were taxonomically identical, except for the A-H1N1 subtype in 1997 (vaccine: A/Beijing/262/95, titration: A/Johannesburg/33/94).

Year	A-H3N2	A-H1N1	B
1996	Nanchang/933/95	Texas/36/91	Harbin/7/94
1997	Nanchang/933/95	Beijing/262/95	Harbin/7/94
1998	Sydney/5/97	Beijing/262/95	Harbin/7/94
1999	Sydney/5/97	Beijing/262/95	Yamanashi/166/98

2.2. Serum antibody titers

Hemagglutination inhibition assays (HIA) were performed using a single stock source for each of the hemagglutinin antigens (supplied by Centers for Disease Control) and representing the strains of virus contained in the vaccine. HIA was performed as previously described [19] using two-fold dilutions of serum from 1/10 to 1/1024. Titers of <1/10 were calculated as 1/5. Geometric mean titers were calculated using log conversion for each dilution.

2.3. Linear regression models

Heteroscedasticity robust ordinary least squares, a type of linear regression model, was used to determine the effects of age and vaccination history on individual post-vaccination titers, T_{post}, using the heteroskedasticity robust regression (option r) in Stata 12 software. In all calculations pre- and post-vaccination HI titers (T_{pre}- and T_{post}-values) were log_2-transformed logarithms of measured titer levels. For an undetectable HI titer (<10, indicating a 'seronegative' person), a value of 5 was imputed. Group log titer means were re-exponentiated and presented as geometric mean titers GMTs throughout the text.

The initial regression model was $T_{post} = A + B_{pre} * T_{pre}$, where A is the y-axis intercept, T_{pre} the pre-vaccination titer, and B_{pre} the regression coefficient (additional increase in T_{post} per unit increase of T_{pre}). Subsequently, age group (G: young adults = 0, elderly adults = 1) and number of vaccinations within the study (NV: values from 1 to 4) were then added to the regression models as independent variables: $T_{post} = A + B_{pre} * T_{pre} + B_{agegroup} * G$ and $T_{post} = A + B_{pre} * T_{pre} + B_{agegroup} * G + B_{nv} *$ NV. The respective regression coefficients were designated $B_{agegroup}$ and B_{nv}. All analyses were run for the three virus (sub)types separately, and for all (sub)types combined.

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