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Frailty is associated with impairment of vaccine-induced antibody response and increase in post-vaccination influenza infection in community-dwelling older adults

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Abstract

Annual immunization with a trivalent inactivated vaccine (TIV) is considered efficacious for prevention of seasonal influenza in older adults. However, significant controversy exists in the current literature regarding the clinical effectiveness of TIV immunization in this highly heterogeneous population. Frailty is an important geriatric syndrome characterized by decreased physiologic reserve and increased vulnerability to stressors. Using a validated set of frailty criteria, we conducted a prospective observational study to evaluate TIV-induced strain-specific hemagglutination inhibition (HI) antibody titers and post-vaccination rates of influenza-like illness (ILI) and infection in frail and nonfrail older adults. The results indicate that frailty was associated with significant impairment in TIV-induced strain-specific HI titers and increased rates of ILI and laboratory-confirmed influenza infection. These findings suggest that assessing frailty status in the elderly may identify those who are less likely to respond to TIV immunization and be at higher risk for seasonal influenza and its complications.

Keywords

Frailty; Influenza immunization; Antibody response; Influenza infection; Influenza-like illness; Older adults

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1. Introduction

Seasonal influenza causes significant morbidity and mortality in older adults [1–3]. A large number of studies have shown the efficacy of annual immunization with TIV (Cochrane Database Systemic Review) [4], which is the current vaccination strategy against influenza infection in this population. For example, the efficacy of TIV immunization in relatively young and healthy seniors has been demonstrated by controlled trials [5,6] and prospective observational studies [7,8]. Nichol and colleagues have shown the effectiveness of annual TIV immunization in working adults aged 50–64 years as well as in the elderly [9–12]. However, Simonsen et al. reported that increased vaccination coverage over the past 2 decades failed to reduce influenza-related mortality in older adults [13–15]. A nested case–control study, with the majority of its study population being over 70 years, demonstrated no significant benefit of TIV immunization against pneumonia secondary to influenza infection [16]. Impaired functional status has also been associated with decreased mortality benefit of TIV immunization in the elderly [17]. These studies suggest significant controversy in the current literature regarding the clinical effectiveness of TIV immunization in this highly heterogeneous population as well as the need for further evaluation of the effectiveness of TIV immunization in subsets of seniors who are older and frail.

Frailty is an important geriatric syndrome characterized by decreased physiologic reserve and increased vulnerability with multi-system dysregulation, leading to hospitalization, dependency, and early mortality in older adults [18–21]. A 5-item set of criteria has been validated in multiple studies to identify seniors who are frail and vulnerable to adverse health outcomes in the community [18,21–24]. Based on these criteria, frailty has an estimated prevalence of 7% among community-dwelling men and women 65 years and older, and up to 30% in those over 80 years [18,23]. Evidence from our group and others suggests that frail older adults manifest a heightened inflammatory state and significant dysregulation in the innate and T cell compartments that appear to be above and beyond age-related senescent immune remodeling [22,25–31]. However, potential impact of frailty on TIV-induced antibody response and its clinical effectiveness in the elderly population has not been adequately investigated.

The objective of this study was to evaluate TIV-induced strain-specific HI antibody titers as well as post-vaccination rates of influenza-like illness (ILI) and laboratory confirmed influenza infections in frail and nonfrail older adults. We hypothesized that frail older persons would have lower HI titers to TIV immunization and higher post-vaccination rates of ILI and laboratory-confirmed influenza infections than nonfrail controls. The results indicate that assessing frailty status in the elderly may identify those who are less likely to respond to TIV immunization and be at higher risk for seasonal influenza and its complications.

2. Materials and methods

2.1. Study design and participants

This is a prospective observational study of the potential influence of the frailty syndrome on strain-specific antibody response and clinical effectiveness of influenza immunizations with TIV in older adults. The study was performed during 2007–2008 influenza season. Community-dwelling older adults over 70 were recruited via collaborating physicians and community newspaper advertisement and flyers at outpatient clinics, senior centers, retirement communities, and residential areas in Baltimore, Maryland. Potential candidates who consented to participate were screened by trained clinical research coordinators according to the validated frailty criteria (see below). Information about clinical diagnosis,

medication usage, and TIV immunization in the previous 5 influenza seasons was obtained by self-report and confirmed by review of medical records with participants' permission from their primary care physician's offices. Exclusion criteria included allergies to eggs or influenza vaccine components, acute illness such as a viral infection or acute exacerbation of chronic conditions, recent use (within past year) of immune modulating agents (glucocorticoid steroids, methotrexate, etc.), rheumatoid arthritis or other systemic inflammatory conditions, active malignancy or on radiation or chemotherapy, uncompensated congestive heart failure or endocrine disorders, Parkinson's disease, dementia, or stroke with residual hemiparesis. These exclusion criteria were designed to eliminate any contraindications for vaccine and minimize confounding immune effects of existing medical conditions or medications. They also addressed the possibility that specific diseases would mimic or overshadow the frailty phenotype. These enrollment criteria (except for allergies to eggs or influenza vaccine) have been successfully applied in our previous frailty studies [25,32]. The Johns Hopkins Institutional Review Board approved the study protocol, and written informed consent was obtained from all participants.

2.2. Determination and classification of frailty

Participants were categorized as frail, prefrail, and nonfrail according to the validated and widely utilized frailty criteria [18]. This set of criteria is based on the presence or absence of five measurable characteristics: slowed motor performance (by walking speed), poor endurance and energy (by self-report of exhaustion), weakness (by grip strength), shrinking (by unintentional weight loss), and low physical activity. Older persons with three or more out of these five characteristics were defined as frail, those with one or two as prefrail, and those with none as nonfrail.

2.3. TIV immunization

As shown in Fig. 1, study participants were recruited in early October 2007, 3–4 weeks before the peak influenza immunization in the Baltimore area (late October). After initial screening, eligible candidates with written informed consent came to the General Clinical Research Center (GCRC) at Johns Hopkins Bayview Medical Center (JHBMC), now the Johns Hopkins Institute of Clinical and Translational Research, or were seen at home if they preferred. They underwent pre-vaccination evaluation and vaccine administration (Visit 1). Commercially available standard TIV of 2007–2008 formula supplied as a 0.5mL dose in a pre-filled syringe (Fluarix, GlaxoSmithKline) containing 15mcg of hemaglutinin for each of the following 3 strains, A/Solomon Islands/3/2006 (H1N1), A/Wisconsin/67/2005 (H3N2), and B/Malaysia/2506/2004, was administered by intramuscular injection by a licensed health-care provider. During the 4th week after TIV immunization, participants returned to the GCRC at JHBMC or were seen at home for a post-vaccination evaluation (Visit 2). Serum samples were collected at each visit and stored at −80 °C for pre- and post-vaccination antibody titer measurements.

2.4. Influenza surveillance during post-vaccination season

Participants were instructed to report any influenza-like symptoms by calling a central phone number with recording capability 24 h a day, 7 days a week throughout the post-vaccination season. Anyone who called to report symptoms was contacted immediately by the research team to ask the participants (or their family member to help) to take a body temperature (if not already done so) and confirm the participants' symptoms and signs. In addition, all participants were contacted weekly by phone and asked a series of questions regarding their general health status and the presence of such symptoms and signs. Clinical cases of ILI were defined by either (i) presence of fever (100 °F orally or 101 °F rectally) plus one or more of the following: cough, headache, myalgias, or sore throat [33]; or (ii) in the absence of fever, the occurrence of two or more of the following symptoms: cough,

coryza, sore throat, myalgia, headache, or photophobia [34,35]. Participants whose symptoms and signs met the above diagnostic criteria for ILI were visited by the research team 3–4 weeks after the onset of ILI to obtain a post-ILI serum sample for post-ILI serology. Influenza infection was confirmed based on the serology criterion of a 4-fold or more rise in post-ILI strain-specific antibody titer. Influenza surveillance was conducted over a period of 27 weeks and was discontinued on Friday, May 2, 2008, about 4 weeks after the last influenza case of the season was reported in the Baltimore area.

2.5. Measurement of strain-specific anti-influenza antibody titers

Strain-specific anti-influenza antibody titers against hemagglutinin (HA) were measured using hemagglutination inhibition (HI) assay. Appropriate influenza reference antigens and anti-sera were obtained from the WHO Collaborating Center for Influenza, the Center for Disease Control and Prevention (Atlanta, GA). All freshly thawed serum samples were pre-treated with receptor destroying enzyme (RDE) (Denka Seiken, Tokyo, Japan) and by pre-adsorption with turkey red blood cells (RBC) (RDI Division of Fitzgerald Industries International, Concord, MA) to remove non-specific inhibitors and agglutinin, respectively. After careful titration of reference antigens against turkey RBC (0.5%) and treated reference sera, HI antibody titers were measured using V-shaped 96-well microtiter plates, according to the standard microtiter technique [36]. Paired pre- and post-vaccination serum samples as well as post-ILI serum samples (for those who had ILI) from the same subject were analyzed simultaneously for HI antibodies against each of the three vaccine strains. HI titers were recorded as the reciprocal of the highest serum dilution that produced complete inhibition of RBC agglutination.

2.6. Data analysis

Summary statistics of demographic and clinical characteristics were constructed for all study participants and distributions these characteristics were summarized across the nonfrail, prefrail, and frail groups and across the groups of participants with no ILI, ILI cases, and influenza cases. Geometric mean of HI titers (GMT) and standard deviations were presented. Comparisons between log-transformed HI titers pre- and post-immunization HI titers were analyzed by paired *t*-tests. Seroprotection was defined by post-immunization HI titer equal or greater than 1:40; seroconversion was defined by 4-fold or high post- over pre-immunization increase in HI titers; and rates of seroprotection and seroconversion were obtained in all participants as well as in individual study groups. GMT titer ratio was calculated as post-immunization GMT titer divided by pre-immunization GMT titer. The Jonckheere–Terpstra tests were used to determine statistical significance of stepwise increase/decrease trends in log-transformed HI titers and GMT ratios across the study groups. Fisher exact tests were performed to determine statistical significance of differences in rates of sero-protection or seroconversion between nonfrail and frail groups or between the groups of participants with no ILI and influenza cases. The Cochran–Armitage tests were used to determine statistical significance of stepwise increase/decrease trends in overall rates ILI or influenza infection during post-vaccination season across the study groups. Results from our exploratory analysis showed no significant difference in all demographic and clinical characteristics across the frailty study groups except for age. To assess the effect of frailty independent of age, linear regressions were used to model log-transformed HI titers, GMT ratios; logistic regressions were used to model post-vaccination rates of ILI and influenza infection. Intercooled Stata software, version 9 was used for model estimation and diagnostics (Stata Corporation, College Station, TX).

3. Results

3.1. Characteristics of the study participants

Of 94 persons initially screened, 78 (83%) met the eligibility criteria and enrolled into the study. Seven individuals were lost follow-up due to either moving out of the area for the winter season (n = 4), refusal of providing a post-vaccination blood specimen (n = 2), or being hospitalized after an accidental fall and subsequent death (n = 1). This yielded a final sample size of 71 (91% of the total enrolled). Table 1 summarizes major demographic and clinical characteristics of the study population and across the frail (n = 17), prefrail (n = 32), and nonfrail (n = 22) groups. The mean age of the participants was 84.5 years with a range of 72–95. The majority of the participants were female and Caucasian with education level of high school and above. Participants had an average of 3–4 chronic diseases including hypertension, other cardiovascular diseases (coronary artery disease, congestive heart failure, atrial fibrillation, and stroke), hyperlipidemia, osteoarthritis, and hypothyroidism. On average, participants took 3–4 commonly prescribed medications, such as diuretics, HMG-CoA reductase inhibitors, β-blockers, thyroid hormone supplement, and ACE-inhibitors. Consistent with previously reported prevalence of frailty in older adults over 80 years of age [18,23], 17 (24%) subjects were frail. Compared with nonfrail controls, frail participants were older (86.0±3.1 *vs.* 82.0±5.4, p = .01). No significant difference was observed between frail and nonfrail participants in race, sex, education, BMI, total number of medical diagnoses or specific chronic conditions, and total number of medications or usage of specific drugs. All participants had TIV immunization in each of the prior 5 influenza seasons.

3.2. TIV-induced strain-specific antibody response in all participants and across the frailty study groups

As shown in Table 2, the study population as a whole "All (n = 71)" had significantly higher post-immunization HI titers compared to pre-immunization HI titers to H1N1, H3N2, and B strains (GMT titers [Mean±geometric SD]: 308±2.1 *vs.* 174±2.1, p = .001; 408±2.6 *vs.* 279±2.2, p = .01; 85±1.8 *vs.* 78±1.7, p .005, respectively, paired t test), indicating active immunogenicity of the vaccine used in the study. Among the study groups, nonfrail participants had significantly higher post-immunization than pre-immunization HI titers to H1N1, H3N2, and B strains (387±2.0 *vs.* 201±2.0, p < .001; 497±1.9 *vs.* 309±1.6, p < .001; and 105±1.5 *vs.* 88±1.4, p = .01, respectively). Prefrail participants had significantly higher post-immunization than pre-immunization HI titers to H1N1 and H3N2 (282±2.3 *vs.* 157±2.2, p = .01 and 388±2.4 *vs.* 278±2.1, p = .01, respectively). The difference between post-immunization and pre-immunization HI titers to B strain in these participants was not statistically significant (81±1.3 *vs.* 78±1.6, p = .23). In contract, there was no statistically significant difference between post-immunization and pre-immunization HI titers to any of the above vaccine strains among frail participants (201±2.1 *vs.* 149±1.9 to H1N1, p = .43; 307±2.3 *vs.* 255±2.0 to H3N2, p = .17; and 67±2.1 *vs.* 65±2.0 to B, p = .33, respectively). In addition, post-immunization HI titers to all three vaccine strains had significant stepwise decrease from the nonfrail and prefrail to the frail participants, adjusted for age (387±2.0, 282±2.3, 201±2.1, respectively, to H1N1, p = .03; 497±1.9, 388±2.4, 307±2.3, respectively, to H3N2, p = .02; and 105±1.5, 81±1.3, 67±2.1, respectively, to B, p = .05).

Next, we examined rates of seroprotection and seroconversion. Seroprotection is conventionally defined by post-immunization HI titer equal or greater than 1:40. The rates of seroprotection were high to all three strains in the study population (94%, 92%, and 82% to H1N1, H3N2 and B strain, respectively) and they did not differ among nonfrail, prefrail and frail study groups (Table 2). Serocon-version is defined by 4-fold or higher post- over pre-immunization HI titer rise. The rates of seroconversion were low to all three strains in

the study population [7% (5 participants), 13% (9), and 1% (1) to H1N1, H3N2 and B strain, respectively)]. Among the study groups, nonfrail participants had seroconversion rates of 13% (3 participants), 27% (6) and 5% (1) to H1N1, H3N2 and B strain, respectively; prefrail participants had seroconversion rates of 6%, 6%, and none, respectively; while only 6% (1) frail participants was seroconverted to H3N2 and none to H1N1 or B (Table 2). The difference in rates of seroconversion to H3N2 between nonfrail and frail groups was statistically significant (27% *vs.* 6%, respectively, $p = .05$, Fisher exact test).

We also evaluated the GMT titer ratios for TIV-induced anti-body response in all participants and among three study groups. As shown by Fig. 2, GMT ratios in all participants were 1.5, 1.7, and 1.4 to H1N1, H3N2, and B, respectively. Among the study groups, GMT ratios to all three vaccine strains had significant stepwise decrease from the nonfrail and prefrail to the frail participants, adjusted for age (1.6, 1.3, 1.1, respectively, to H1N1, $p = .04$; 1.9, 1.6, 1.1, respectively, to H3N2, $p = .01$; and 1.5, 1.3, 1.1, respectively, to B, $p = .05$).

Taken together, these results demonstrate that frailty is associated with significant impairment in antibody responses to TIV immunization among community-dwelling older adults.

3.3. Rates of influenza-like illness (ILI) and confirmed influenza infection

A total of 19 (26.8%) participants developed ILI during the post-vaccination season. Eleven (15.5%) participants were confirmed for influenza infection by post-ILI serology, among which seven cases were influenza A/H3N2, one case of influenza A/H1N1, and three cases of influenza B. Three cases (all influenza A/H3N2) were hospitalized for severe influenza infection and secondary pneumonia and two subsequently died (one from respiratory failure and one from cardiac arrest). As shown in Fig. 3, the rates of ILI and confirmed influenza infection had significant stepwise increase from the nonfrail and prefrail to the frail participants (9%, 25%, and 53%, respectively, $p = .002$ for ILI; 5%, 16%, and 29%, respectively, $p = .02$ for influenza infection). These trends remained statistically significant after adjusting for age ($p = .005$, 0.03 for ILI and influenza infection, respectively). Among three influenza A/H3N2 cases who were hospitalized influenza cases, two were frail (one met 3 and the other met 5 of the 5 frailty criteria) and subsequently died; the other one was prefrail (met 1 of the 5 frailty criteria). The remaining four influenza A/H3N2 cases include two prefrail (both met 1 of the 5 frailty criteria), one frail (met 4 of the 5 frailty criteria), and one nonfrail. The influenza A/H1N1 case was frail (met 3 of the 5 frailty criteria). One influenza B case was frail (met 4 of the 5 frailty criteria) and two were prefrail (met 2 of the 5 frailty criteria for both cases). Regarding the time course of the ILI and influenza cases, the first ILI case occurred in late November, 7 weeks after the participant received TIV administration. The subsequent 9 ILI cases occurred in December, 6 of which were confirmed influenza. The rest were reported in January and February except for one ILI case in early March. These results indicate that despite TIV immunization, frailty is associated with significantly higher rates of ILI and influenza infection during post-vaccination season.

3.4. Demographic characteristics and TIV-induced strain-specific antibody response among participants with no ILI, ILI cases, and serologically confirmed influenza cases

Age did not differ among participants with no ILI, ILI cases, and serologically confirmed influenza cases (mean + SD: 84.3 + 4.9 *vs.* 85 + 3.5 *vs.* 84 + 3.4, respectively, $p = .61$). There was no significant difference in other variables listed in Table 1 among these groups (data not shown). Table 3 summarizes pre- and post-immunization HI titers and rates of seroprotection and seroconversion across the three groups. Participants with no ILI had significantly higher post-immunization than pre-immunization HI titers to all three strains

(378 + 2.3 *vs.* 179 + 2.2, $p = .001$; 468 + 2.7 *vs.* 289 + 2.4, $p = .01$; and 87 + 1.6 *vs.* 79 + 1.3, $p = .04$, respectively). ILI cases had significantly higher post-immunization than pre-immunization HI titers to H1N1 and H3N2 (274 + 2.4 *vs.* 151 + 2.5, $p = .05$ and 389 + 2.6 *vs.* 268 + 2.4, $p = .05$, respectively) and marginally higher post-immunization HI titer to B (82 + 1.5 *vs.* 76 + 1.3, $p = .08$). There was no statistically significant difference between post-immunization and pre-immunization HI titers to any vaccine strains in influenza cases (195 + 2.3 *vs.* 144 + 2.3 to H1N1, $p = .13$; 301 + 2.7 *vs.* 230 + 2.3 to H3N2, $p = .09$; and 66 + 1.4 *vs.* 64 + 1.5 to B, $p = .41$, respectively). Post-immunization HI titers to H1N1 and H3N2 had significant stepwise decrease from the participants with no ILI and ILI cases to the influenza cases (378 + 2.3, 274 + 2.4, 195 + 2.3, respectively, to H1N1, $p = .05$; 468 + 2.7, 389 + 2.6, 301 + 2.7, respectively, to H3N2, $p = .04$). Decrease in that to B strain across these three groups had marginal significance (87 + 1.6, 82 + 1.5, 66 + 1.4, respectively, $p = .07$). Seroprotection rates were high in all three groups and did not differ between the groups. In participants with no ILI, five (10%) were seroconverted to H1N1, eight (15%) were seroconverted to H3N2, and one (2%) was seroconverted to B strain. None of the ILI or influenza cases were seroconverted to H1N1 or B and one ILI case (5%) was seroconverted to H3N2. These results indicate significant difference in overall TIV-induced strain-specific antibody response among participants with no ILI compared to the ILI and influenza cases.

4. Discussion

Here we demonstrate for the first time, the significant impact of the geriatric syndrome of frailty on TIV immunization. Specifically, we have shown that frailty is associated with decreased HI titer response to TIV immunization and increased rates of post-vaccination ILI and influenza infection in community-dwelling older adults. Participants with no ILI had better antibody response to TIV immunization as indicated by significantly higher post-immunization HI titers and most seroconversions than ILI or influenza cases, suggesting a correlation of TIV-induced antibody response with protection against influenza in the study population.

Consistent with the observation of age-related decrease in TIV-induced antibody response reported in the literature (reviewed in references [7,37,38]), the overall antibody response to TIV immunization in this study was poor. The rates of seroconversion to more than one vaccine strains, which were seldom reported in previous studies, were strikingly low; only two participants (2.8%, one non-frail and one prefrail participant) seroconverted to both H1N1 and H3N2; one (nonfrail) seroconverted to both H3N2 and B strains; none had positive seroconversion to all three vaccine strains. It was noted that the pre-immunization HI titers were high, most of which were greater than 1:40. This is likely the result of prior annual vaccination and suggests that a post-immunization titer of 1:40, or seroprotection, as the threshold of immune protection against influenza may not be applicable to these elderly individuals. Nonetheless, TIV-induced antibody response appears to be correlated with clinical protection against influenza as discussed above. This is in contrast to a previous study by Gravenstein and colleagues in a veteran's home setting where no such correlation was observed [39].

The post-vaccination rate of serologically confirmed influenza infection observed in this study is consistent with the influenza infection rate recently reported by Shahid and colleagues in 2007–2008 influenza season [40]. Three hospitalized severe influenza cases were all H3N2 infections, which is consistent with the report by Thompson et al. that H3N2 influenza infections are associated with the highest hospitalization rates in older adults [1]. We used this influenza-specific measure and post-vaccination rate of ILI to minimize confounders associated with all-cause mortality or other outcome measures not specific to seasonal influenza. Moreover, this study specifically targeted to a frail subset of community-

dwelling older adults. Except for age, which was adjusted in our analyses, there was no significant difference in demographic and clinical profiles between frail and nonfrail participants. Of note, several studies evaluated TIV-induced antibody response and/or TIV efficacy in "frail" institutionalized older persons [41–43]. However, despite a specific type of disability or disabilities that require long-term functional and healthcare support, many nursing home residents may not be truly frail and can still mount a robust antibody response to TIV immunization. In fact, a quantitative review of a large number of studies has demonstrated better antibody responses to TIV immunization in nursing home residents compared to those living in the community [38]. In addition, a recent Australian study has shown that incompletely matched influenza vaccine still provided protection among institutionalized older persons [43].

This study has several limitations. First, it has a relatively small sample size. For example, the result of no positive seroconversion to H1N1 or B strains in the frail group could partly be due to this limitation. However, significant stepwise decrease in rates of antibody response and increase in rates of ILI and influenza infection were observed across the nonfrail, prefrail and frail groups. Secondly, new virus strains appeared in the circulation in early 2008, which led to significant reformulation of the 2008–2009 TIV vaccine. As such, laboratory confirmation by post-ILI serology might have underestimated the rate of influenza infection among all ILI cases, particularly those that occurred after January 1, 2008. In addition, no data is available on TIV-induced cell-mediated immunity (CMI) from this study. Other studies have shown CMI as an important part of TIV-induced immunity against influenza in older adults [8,44,45], and further investigations into potential impact of frailty on CMI are warranted. While two frail participants were hospitalized for severe influenza and secondary pneumonia and subsequently died, we did not intend to recruit frail older individuals who had terminal illness as their frailty phenotype could be driven by a single terminal illness. Recognizing these limitations and the need for further confirmation and expansion, findings from this study provide initial evidence suggesting that assessing frailty status in the elderly may identify those who are less likely to respond to TIV immunization and be at higher risk for seasonal influenza and its complications. These results also emphasize the need for more targeted and effective influenza immunization and preventive strategies for this vulnerable community-dwelling elderly population.

Abbreviations

TIV	trivalent inactivated vaccine
ILI	influenza-like illness
HA	hemagglutinin
HI	hemagglutination inhibition

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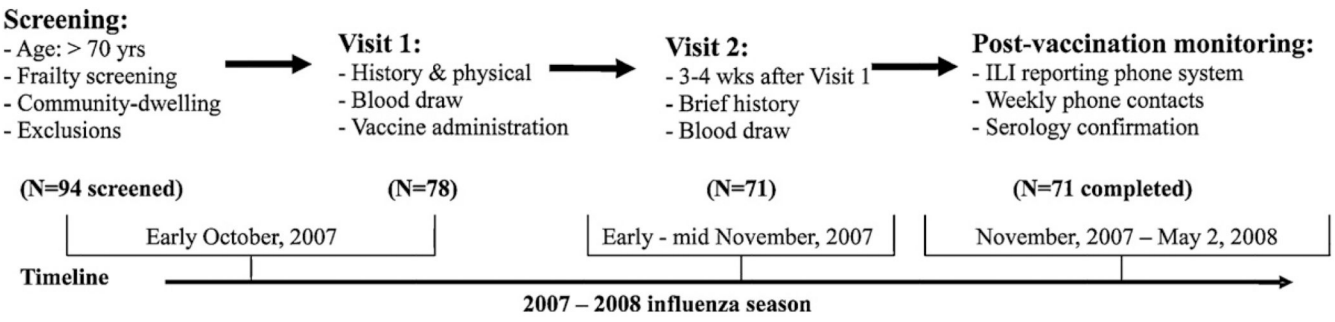

Fig. 1.

Pre-vaccination screening and blood draw, TIV immunization, as well as post-vaccination blood draw and influenza surveillance.

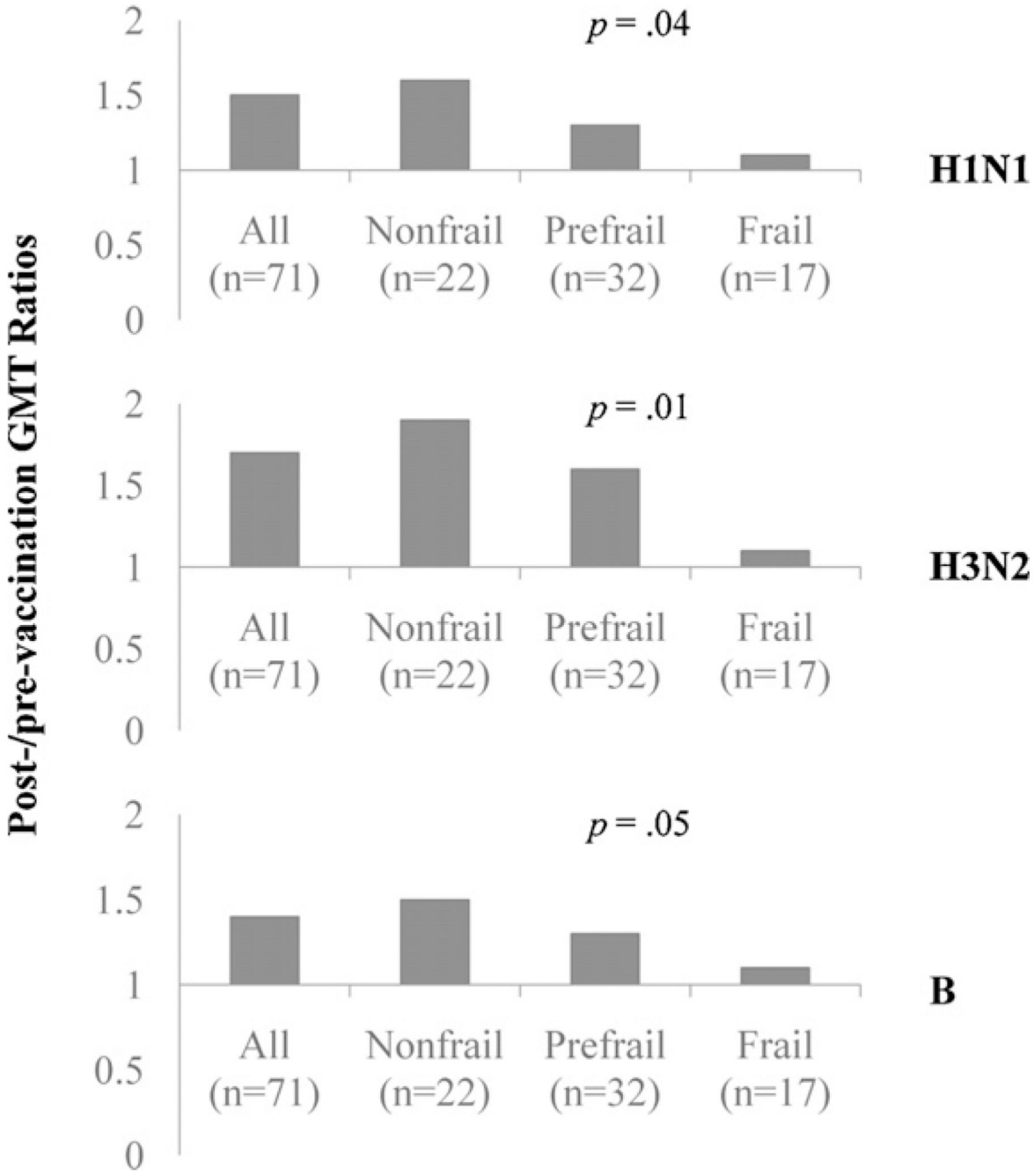

Fig. 2.

GMT ratios to H1N1, H3N2, and B strains in all study participants "All (*n* = 71)", nonfrail (*n* = 22), prefrail (*n* = 32), and frail (*n* = 17) groups. *p* Values were derived from linear regression analysis for stepwise trend of decrease in nonfrail, prefrail, to frail study groups, adjusted for age.

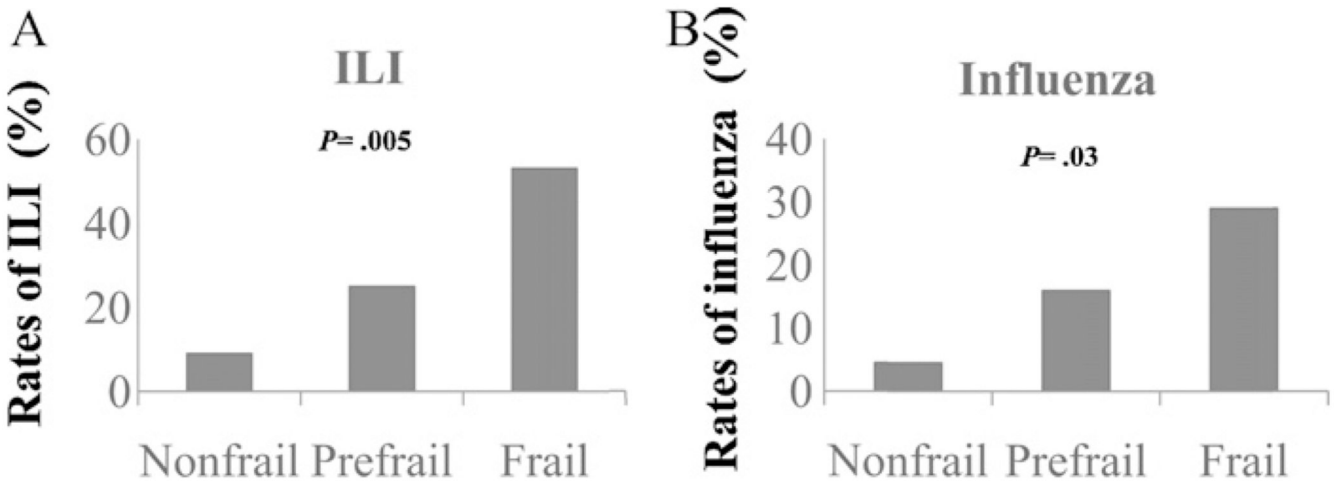

Fig. 3.

Rates of influenza-like illness (ILI) (A) and laboratory confirmed influenza infection (B) during post-vaccination season. *p* Values were obtained from logistic regression analysis for stepwise trend of increase in nonfrail, prefrail, to frail study groups, adjusted for age.

Table 1

Demographic and clinical characteristics and study variables in all study participants and across the frailty spectrum.

Variables	All subjects (*n* = 71)	Nonfrail (*n* = 22)	Prefrail (*n* = 32)	Frail (*n* = 17)	*p*[a]
Age (years), mean (SD[+])	84.5 (4.6)	82.0 (5.4)	85.4 (4.1)	86.0 (3.1)	.01
Race (white), %	91.6%	95.5%	90.6%	88.4%	.14
Sex (female), %	77.5%	81.8%	68.8%	88.2%	.68
Education (high school or above), %	94.4%	100.0%	93.7%	88.2%	.42
BMI (kg/m^2), mean (SD)	25.0 (4.2)	25.0 (3.0)	24.5 (3.2)	25.9 (7.0)	.47
Total # chronic diseases, mean (SD)	3.7 (1.5)	3.2 (1.3)	3.8 (2.4)	4.1 (4.5)	.43
Common clinical conditions					
Hypertension, %	67.1%	81.0%	59.4%	64.7%	.29
Other cardiovascular disease, %	38.0%	27.3%	46.9%	35.3%	.79
Hyperlipidemia, %	54.9%	59.1%	59.4%	41.2%	.34
Osteoarthritis, %	29.6%	22.7%	28.1%	41.2%	.30
Hypothyroidism, %	23.9%	22.7%	25.0%	23.5%	.98
Total # medications, mean (SD)	3.3 (1.5)	3.5 (2.4)	3.0 (2.8)	4.2 (5.3)	.34
Commonly used medications					
Diuretics, %	47.9%	54.6%	43.8%	47.1%	.75
HMG-CoA reductase inhibitor (lipid-lowering drugs), %	43.7%	50.0%	43.8%	35.3%	.52
β-Blockers, %	32.4%	31.8%	34.4%	29.4%	.94
Thyroid hormone supplement, %	29.0%	27.3%	31.3%	26.7%	.93
ACE-inhibitors, %	21.1%	27.3%	18.8%	17.7%	.69

[a]Determined using *Fisher exact* test for categorical variables or *t* test for continuous variables between frail and nonfrail participants.

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Table 2

Pre- and post-TIV immunization HI titers and seroprotection or seroversion rates to H1N1, H3N2, and B vaccine strains in all study subjects and across the nonfrail, prefrail, and frail study groups.

HI antibody responses	All subjects (*n* = 71)	Nonfrail (*n* = 22)	Prefrail (*n* = 32)	Frail (*n* = 17)	*p* values
H1N1					
Pre-immunization HI titers[a]	174±2.1	201±2.0	157±2.2	149±1.9	.17*
Post-immunization HI titers[a]	308±2.1	387±2.0	282±2.3	201±2.1	.03*
Pre- *vs.* post- *p* values[b]	.001	<.001	.01	.43	.86**
Seroprotection rates[c]	94%	95%	94%	96%	ND
Seroconversion rates[d]	7%	13%	6%	0	
H3N2					
Pre-immunization HI titers[a]	279±2.2	309±1.6	278±2.1	255±2.0	.16
Post-immunization HI titers[a]	408±2.6	497±1.9	388±2.4	307±2.3	.02*
Pre- *vs.* post- *p* values[b]	.01	.001	.01	.17	.71**
Seroprotection rates[c]	92%	91%	94%	88%	.05**
Seroconversion rates[d]	13%	27%	6%	6%	
B					
Pre-immunization HI titers[a]	78±1.7	88±1.4	78±1.6	65±2.0	.19*
Post-immunization HI titers[a]	85±1.8	105±1.5	81±1.3	67±2.1	.05*
Pre- *vs.* post- *p* values[b]	.005	.01	.23	.33	.87**
Seroprotection rates[c]	82%	86%	78%	82%	ND
Seroconversion rates[d]	1%	5%	0	0	

ND: not done.

*These *p* values derived from linear regression analysis adjusted for age.

**These *p* values derived from Fisher exact test between nonfrail and frail groups.

[a]Mean±geometric SD of geometric mean titers (GMT).

[b]These *p* values derived from paired *t* tests of the pre–post immunization difference in log transformed HI titers.

[c] Seroprotection defined by post-vaccination HI titer≥1:40.

[d] Seroconversion defined by 4-fold or higher HI titer increase after TIV immunization or post- over pre-vaccination HI titer ratio ≥4.

Table 3

Pre- and post-TIV immunization HI titers and seroprotection or seroversion rates to H1N1, H3N2, and B vaccine strains in subjects without ILI and in influenza or ILI cases.

HI antibody responses	Subjects with no ILI (*n* = 52)	ILI cases (*n* = 19)	Influenza cases (*n* = 11)	*p* values
H1N1				
Pre-vaccination titers[a]	179±2.2	151±2.5	144±2.3	.17*
Post-vaccination titers[a]	378±2.3	274±2.4	195±2.3	.05*
Pre- *vs.* post- *p* values[b]	.001	.05	.13	.74**
Seroprotection rates[c]	98%	89%	91%	ND
Seroconversion rates[d]	10%	0	0	
H3N2				
Pre-vaccination titers[a]	289±2.4	268±2.4	230±2.3	.16*
Post-vaccination titers[a]	468±2.7	389±2.6	301±2.7	.04*
Pre- *vs.* post- *p* values[b]	.01	.05	.09	.43**
Seroprotection rates[c]	96%	84%%	91%	ND
Seroconversion rates[d]	15%	5%	0%	
B				
Pre-vaccination titers[a]	79±1.3	76±1.3	64±1.5	.19*
Post-vaccination titers[a]	87±1.5	82±1.5	66±1.4	.07*
Pre- *vs.* post- *p* values[b]	.04	.08	.41	.89**
Seroprotection rates[c]	83%	89%	82%	ND
Seroconversion rates[d]	2%	0	0	

ND: not done.

* These *p* values derived from Jonckheere–Terpstra trend tests across participants with no ILI, ILI cases, and serologically confirmed influenza cases.

** These *p* values derived from Fisher exact test between subjects with no ILI and influenza cases.

[a] Mean±geometric SD of geometric mean titers (GMT).

[b] These *p* values derived from paired *t* tests of the pre–post immunization difference in log transformed HI titers.

[c] Seroprotection defined by post-vaccination HI titer≥1:40.

[d] Seroconversion defined by 4-fold or higher HI titer increase after TIV immunization or post- over pre-vaccination HI titer ratio ≥4.