PERSPECTIVE

Rapid Decline of Influenza Vaccine–Induced Antibody in the Elderly: Is It Real, or Is It Relevant?

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Advisory committees have cautioned that influenza vaccine–induced antibody declines more rapidly in the elderly, falling below seroprotective levels within 4 months. We conducted a literature review to assess this assertion. The articles that were included in this review reported antibody levels ⩾4 months after influenza immunization in persons ⩾60 years old, interpretable in the context of annual influenza vaccine–approval criteria (seroprotection/seroconversion) specified by the Committee for Proprietary Medicinal Products (CPMP) for the elderly. The final review included 14 studies; 8 of which reported seroprotection rates. Seroprotection exceeding CPMP criteria was maintained ⩾4 months after influenza immunization in all 8 of the studies reporting this for the H3N2 component and in 5 of the 7 studies reporting this for the H1N1 and B components. In determining whether CPMP criteria were met at season's end, primary antibody response appeared to be more relevant than secondary antibody decline. Both studies reporting seroprotection rates that failed CPMP criteria ⩾4 months after influenza immunization for each of the H1N1 and B components had also reported failed seroprotection at 1 month after immunization. If initially achieved after immunization, seroprotection rates of 70%–100% were maintained not just at 4 months (2 studies) but also at 5 months (2 studies) and even at >6 months (4 studies), for the H3N2 and H1N1 vaccine components. Seroprotection rates appeared less consistent for the B vaccine component, throughout the postimmunization period. Seroconversion appears to vary substantially and inversely with preimmunization titers but not with age. In 2 of 6 studies reporting seroconversion alone, CPMP criteria were still met at 4 months. In the other 4 studies, the main reason for failure at 4 months was primary failure at 1 month. A total of 6 studies compared antibody persistence by age, and no consistent differences were found on that basis. The historic concern that the influenza vaccine–induced antibody response in the elderly declines more rapidly and below seroprotective levels within 4 months of immunization should be reconsidered.

Influenza immunization programs are timed to optimize protection during an influenza season that, in the northern hemisphere, occurs variably each year between November and April. Antibody response to the 3 components (A/H3N2, A/H1N1, and B) of the trivalent influenza vaccine is measured by the hemagglutination inhibition (HI) test, with a protective threshold conventionally defined as being a reciprocal HI titer ⩾40 [1–8], which is achieved ~2 weeks after immunization, with peak levels achieved at 4–6 weeks [1].

Because of their higher risk of incurring serious complications from influenza, the elderly have long been priority recipients of influenza vaccine, especially during periods of uncertain or limited vaccine supply [9, 10]. Despite prioritization, the elderly in North America have also been cautioned not to receive influenza vaccine too early in the fall. Since at least 1990, the United States' Advisory Committee on Immunization Practice (ACIP) has cautioned that influenza vaccine–induced antibody declines more rapidly in the elderly, notably in the institutionalized, than in young adults and that vaccination before October therefore should be avoided [11, 12]. In Canada, beginning in 1994, the National Advisory Committee on Immunization (NACI) also cautioned that immunization before November should be avoided [13] and, as recently as the 2006–2007 season, continued to caution that "antibody levels may fall below protective levels within 4 months" in the elderly [14]. These precautions have made it difficult to time the immunization of the elderly to provide protection spanning the entire season. During the 2006–2007 season in Canada, for example, the majority of influenza vaccines were delayed until November [15]. When limited amounts became

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Table 1. Guidance on harmonization of requirements for influenza vaccines specified by the Committee for Proprietary Medicinal Products, based on sera collected at baseline and 3 weeks after immunization [6].

Immunogenicity criterion	Definition	Young adults (18–60 years of age)	Elderly (>60 years of age)
Seroprotection rate, %	Proportion achieving reciprocal HI titer of ⩾40	>70	>60
Mean geometric increase[a]	*n*-fold increase above baseline, in geometric mean titers	>2.5	>2.0
Seroconversion rate, %	Proportion with ⩾4-fold rise above baseline HI titers *or* an increase from negative prevaccination to seroprotection levels ⩾40[b]	>40	>30

NOTE. HI, hemagglutination inhibition.

[a] Seroconversion factor was not specifically reported by most studies, and individual titers were not cited to enable derivation of mean geometric increase based on individual ratios relative to baseline. Seroconversion factor was thus estimated as the approximate *n*-fold increase in group geometric mean titers above baseline, indicating whether or not this clearly exceeded 2.

[b] Most studies reporting this did so in terms of proportion showing a 4-fold rise

available during October, some health authorities were reluctant to use this supply to begin immunizing institutionalized elderly, citing, as their rationale, the NACI's concern about late-season loss of seroprotection (British Columbia Communicable Disease Policy Committee, 19 September and 12 December 2006).

No reference has ever been cited by the NACI to support its concern, although the ACIP previously had cited 2 studies. Paradoxically, both ACIP studies included only community-dwelling persons, most of whom were <55 years old, and showed stable antibody responses through to late spring [16, 17]. Between 2002 and 2006, the ACIP discontinued citation of these 2 studies and began to cite a third. The primary objective of this third study was to assess cell-mediated response to influenza vaccination in ~60 institutionalized elderly persons [18]. After an initial modest (<2-fold) rise in antibody titer, that study reported a small but statistically significant decline in geometric mean titers (GMTs) between 6 and 12 weeks after vaccination. A high proportion of participants had been immunized previously, but the proportion with seroprotective antibody levels was not reported initially or subsequently after immunization.

Although there is no doubt that antibody titers decline with time after influenza immunization, the clinical importance of that decline in the elderly, relative to the young and in the context of protection lost or maintained throughout the influenza season, has not been well characterized. We therefore conducted a literature review, to describe the pattern of meaningful antibody decline in the elderly.

METHODS

In 1997, serologic guidelines established by the Committee for Proprietary Medicinal Products (CPMP) of the European Medicines Evaluation Agency were initiated to harmonize the interpretation of influenza vaccine immunogenicity [6, 7]. In the United States, the Food and Drug Administration has adapted CPMP guidelines for the purpose of initial licensure of vaccine, but repeat immunogenicity evaluation is not an annual requirement of reformulated product [8]. Regulatory authorities in Europe and Canada, however, apply CPMP guidelines both to initial licensure of new influenza vaccine and to the approval of reformulated product each year. Separate preseason cohorts of at least 50 young adults (18–60 years of age) and 50 elderly persons (>60 years of age) are assessed, at baseline and at 3 weeks after immunization, to determine their antibody response to influenza vaccine. Reformulated seasonal vaccine is then approved for mass distribution in Europe and Canada when these separate cohorts have met at least 1 of 3 age-specific CPMP criteria for each vaccine component (table 1). A satisfactory antibody response in the elderly cohort is based on either (1) >60% achieving a reciprocal HI titer of ⩾40 (seroprotection rate) or (2) a mean geometric increase in titers of >2.0-fold (seroconversion factor), or (3) >30% achieving a 4-fold rise in antibody titer (seroconversion rate) [6]. Because influenza vaccines for the elderly are reviewed annually in this way, we used these criteria as the primary frame of reference to interpret antibody levels >4 months after immunization. We also assessed whether elderly study participants met the CPMP thresholds established for younger adults, both initially and >4 months after immunization (table 1). Seroconversion factor was not specifically reported by most studies, and individual titers were not cited to enable derivation of mean geometric increase based on individual ratios relative to baseline. Seroconversion factor was thus estimated as the approximate *n*-fold increase in group GMTs above baseline, indicating whether or not this clearly exceeded 2.

Studies reported in the English language were identified by searching the PubMed or EMBASE databases, using combinations of the following terms: influenza vaccine; elderly; aged; older adults; immunogenicity; antibody, and antibody + (persistence, response, titer, blood level, detection or long-term). Additional studies were identified by examining reference lists and consulting key experts. Article titles and abstracts were

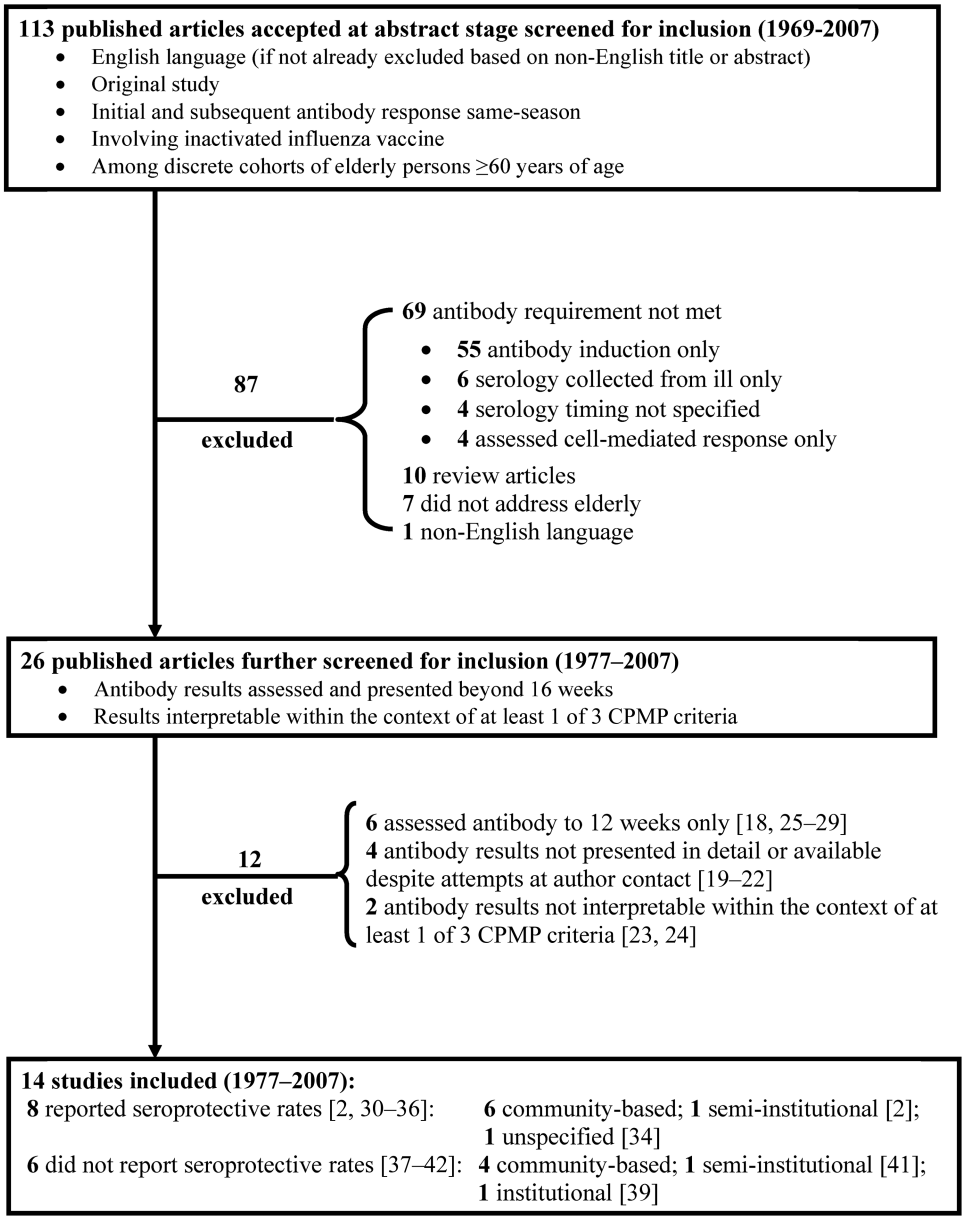

Figure 1. Published articles included in the present review

reviewed for whether or not they addressed serologic response to influenza vaccine in the elderly. Subsequent inclusion criteria required that a publication (1) be an original study of inactivated influenza vaccine involving discrete cohorts of elderly persons ⩾60 years of age, (2) assess antibody levels initially and, within the same season, to at least 16 weeks after immunization, and (3) present results interpretable in the context of at least 1 of 3 CPMP criteria. As the most clinically relevant indicator, we stratified studies on the basis of whether seroprotection rates were reported.

RESULTS

An initial search identified 494 citations. Articles accepted at the abstract stage (113) were reviewed by 2 researchers (D.M.S. and S.A.T.); 87 did not meet initial inclusion criteria (figure 1). Of the 26 articles that met the initial inclusion criteria, an additional 12 were excluded (figure 1) [18–29]. The 14 remaining studies, included in the present review, are summarized in tables 2 and 3 [2, 30–42].

Studies reporting antibody results that provided seroprotection rates. Findings from 8 studies that reported seroprotection rates ⩾4 months after influenza immunization are described below in chronological order and in tables 2 and 4 and figure 2*A*.

Mackenzie [30] reported antibody responses to H3N2 at baseline and at 4, 7, 30, and 50 weeks, in community-dwelling young and elderly participants who re-

Table 2. Studies assessing influenza vaccine–induced antibody in elderly at ⩾16 weeks, with seroprotective rates.

Study	Year	Design	Populations studied	Underlying conditions addressed[a]	Vaccine dose and formulation	No.	Age, average (range), years	Serology intervals, weeks	Previous vaccination addressed	Influenza infection addressed
MacKenzie (1977) [30]	1973–1974	Cohort	Adults[b] (15–59 years) and elderly[b] ⩾60 years	No	2 doses (4 weeks apart) bivalent (16 μg A/H3N2, 8 μg B) subunit deep SQ	231; 69	43; 67	0, 4, 7, 30, 50	No	No
Peters et al. (1988) [31]	1985–1986	RCT	Elderly[b] men >70 years	No	15-μg TIV split[c] or same with added B antigen in same or separate arms IM	42; 44; 43	83 (70–96)	0, 4, 20	64% in 15-μg TIV group previously immunized	No
Delafuente et al. (1998) [32]	1991–1992	RCT	Elderly[b] men >60 years	No (all taking anticoagulants)	15-μg TIV split[c] SQ or IM	13 SQ; 13 IM	68	0, 6, 17	No	No
Buxton et al. (2001) [33]	1998–1999	Cohort	Elderly[b] ⩾65 years (1 dose and 2 doses)	Immune-compromised excluded	1 or 2 (at 12 weeks) 15-μg TIV split IM	28 (1 dose); 28 (2 doses)	74; 74	0, 6, 12, 18, 24	Number vaccinations in prior 5 years noncontributory	7% 1 dose with ⩾4-fold-titer increase after 6 weeks excluded
Brydak et al. (2003) [2]	1999–2000	Cohort	Adults[b] and elderly[d] ⩾60 years	No	15-μg TIV split[c] unspecified route	28; 45	34; 77	0, 4, 20	No	No
Ruf et al. (2004) [34]	2002–2003	RCT	Elderly[e] ⩾60 years	Clinically significant abnormalities excluded	15-μg TIV split[c] or MF-59 adjuvanted[c] or virosome-based[c] IM	273; 275; 272	68 (60% >65)	0, 4, 16, 32	Excluded if vaccinated previous season	Excluded if influenza previous season
Praditsuwan et al. (2005) [35]	1998–1999	RCT	Elderly[b] ⩾60 years	Immune-compromised excluded	15-μg TIV split[c] or placebo IM	330 vaccinated; 305 placebo	68; 68	0, 4, 20, 52	No	5% with ILI; 2.5% with serologic evidence infection
Hui et al. (2006) [36]	2003–2004	RCT	Elderly[b] ⩾60 years	Immune-compromised excluded	15-μg TIV split[c] or placebo IM	65 vaccinated; 63 placebo	75; 74	0, 4, 24	<5% immunized prior 5 years	11% symptomatic with ⩾4-fold rise 4–24 weeks

NOTE. ILI, influenza-like illness; IM, intramuscular; RCT, randomized controlled trial; SQ, subcutaneous; TIV, trivalent inactivated vaccine;

[a] Includes conditions that impair immune status and/or treatment with immune-compromising medication(s).
[b] Community-dwelling.
[c] 1 dose.
[d] Semi-institutionalized.
[e] Likely community-dwelling but unspecified.

Table 3. Studies that assesssed influenza vaccine–induced antibody in elderly at ⩾16 weeks, without seroprotective rates.

Study	Year	Design	Populations studied	Underlying Conditions addressed[a]	Vaccine dose and formulation	No.	Age, average or range, years	Serology intervals (weeks unless specified)	Previous vaccination addressed	Influenza infection addressed
McElhaney et al. (1993) [37]	1990–1991	Cohort	Adults[b] and elderly[b] ⩾60 years	Immune-compromised excluded	15-μg TIV whole[c] (1990) or split[c] (1991) route unspecified	1990: 13; 13 1991: 26; 26	1990 (average): 22–32; 71 1991 (average): 22–39; 72	0, 6 (split) or 8 (whole), 12, 24	Vaccination previous season noncontributory	No
Powers (1995) [29] and Powers et al. (1995) [38]	1993–1994	RCT	Elderly[b] ⩾65 years	Immune-compromised excluded	15-μg monovalent H1N1 split[c] or liposome adjuvanted[c] IM	38; 39	77 ± 7	0, 1, 2, 4, 8, 12, 18	No; 90% vaccinated within one, 95% within 5 years	No; immunized June/July
Van Hoecke et al. (1996) [39]	1994–1995	Cohort	Elderly[d] 65–80, 80–90, and 90–100 years	Immune-compromised excluded	15-μg TIV split[c] IM	457 (211; 208; 38)	80	0, 4, 24	No	No
Minutello et al. (1999) [40]	1992–1995	RCT	Elderly[b] ⩾65 years	No	15-μg TIV subunit[c] or MF-59 adjuvanted[c] IM	1992–1993: 92 (46; 46) 1993–1994: 74 (35; 39) 1994–1995: 67 (32; 35)	72; 73	0, 28 days (and 180 days in 1993–1994 and 1994–1995 or 360 days in 1992–1993)	No	Excluded if ⩾4-fold titer rise >4 weeks after immunization
Mysliwska et al. (2004)[e] [41]	1999–2001	Cohort	Adults[b] and elderly[f] ⩾65 years (healthy vs. chronic conditions)	Stratified analysis	15-μg TIV split[c] unspecified route	1999: 98 (70; 28); 142 (46; 96) 2000: 67; 110 (38; 72)	1999–2000: 32; 75 (2000–2001: 19–42; 65–92)	0, 4, 20	None previously vaccinated	32% year 1 and 28% year 2 with RTI; influenza negative
Keylock et al. (2007) [42]	Not specified	Cohort	Elderly[b]⩾60 years (low- vs. high-physical fit)	Immune-compromised excluded	15-μg TIV split[c] IM	26	60–76	0, 6, 36	77% low and 69% high fitness previously vaccinated; effects not described	12% with influenza-like illness none with serologically confirmed influenza

NOTE. IM, intramuscular; RCT, randomized controlled trial; RTI, physician-diagnosed respiratory-tract infection; TIV, trivalent inactivated vaccine.

[a] Includes conditions that impair immune status and/or treatment with immune-compromising medication(s).
[b] Community-dwelling individuals.
[c] 1 dose.
[d] Institutionalized.
[e] In first year, participants overlap with those studied by Brydak et al. (2003) [2].
[f] Semi-institutionalized.

ceived influenza vaccine at 0 and 4 weeks. Although this is not the standard schedule, we include this study for its age-related comparisons. Most studies have shown little or no improvement in the antibody profile of the elderly who received additional doses during the same season [33, 43–48]. In the present study, preimmunization titers in young participants were not different from those in the elderly, and, at 30 and 50 weeks, seroprotective rates were similarly maintained among elderly and young 2-dose recipients (table 4). CPMP criteria based on the seroconversion factor were also exceeded in the elderly at a rate comparable to that in young adults, at 30 weeks (19-fold and 21-fold above baseline, respectively) and at 50 weeks (13-fold each) (table 4). In both cohorts (i.e., the elderly and young adults), higher preimmunization titers were associated with higher rates of seroprotection but lower rates of seroconversion, after immunization.

Peters et al. [31] assessed antibody response at baseline and at 4 and 20 weeks, in community-dwelling elderly men. As in other studies, seroconversion after vaccination decreased with increasing levels of preexisting (baseline) antibody. In participants who received a conventional dose, the CPMP seroprotection rates and the seroconversion factor were met for the H3N2 and B components, at 4 and 20 weeks. At neither interval was the seroprotection-rate criterion for H1N1 met. At 4 weeks, GMTs were >2-fold elevated for the H1N1 component, but this was not so at 20 weeks (table 4 and figure 2*A*). No relationship between age and antibody response was found over the 26-year age span (70–96 years) of the study population.

Delafuente et al. [32] reported antibody responses at baseline and at 6 and 17 weeks, in community-dwelling elderly men receiving oral anticoagulant therapy. The same H1N1 component and an antigenically similar B strain had been included in the previous year's vaccine, whereas the H3N2 component was new. Consequently, high baseline titers and seroprotective rates to the H1N1 and B components, but not the H3N2 component, were observed before immunization (table 4). Delafuente et al. concluded that there was a persistence of the vaccine-induced seroprotective antibody for >1 year after the previous season. Seroprotection rates exceeding the CPMP criterion were then observed for the H1N1 and B components, but not for the H3N2 component, at 6 weeks. At 17 weeks, seroprotection rates were >60% for all 3 components (table 4). Conversely, there was a >2-fold-titer increase above baseline for the H3N2 component, but not for either the H1N1 or B component, at 6 weeks (table 4 and figure 2*A*). Delafuente et al. commented that the high-preimmunization titers may have limited their ability to demonstrate initial seroconversion for the H1N1 and B components. At 17 weeks, a 2-fold increase in GMTs relative to baseline was maintained for the H3N2 component and was also evident for the B component.

In a community-based study of 1- versus 2-dose vaccination of elderly persons, Buxton et al. [33] reported high rates of seroprotection, maintained in both cohorts at week 24, against H3N2 and H1N1 (table 4). Response to the B component was inferior throughout, although >60% at 18 weeks and 56% at 24 weeks maintained seroprotective titers after 1 dose. At 6, 18, and 24 weeks after a single immunization, GMTs against H3N2 and H1N1 were >2-fold above baseline; GMTs against the B component never rose 2-fold, not even initially (table 4 and figure 2*A*).

Brydak et al. [2] reported that, at 4 and 20 weeks after immunization, more semi-institutionalized (i.e., nursing home) elderly than young adults attained seroprotective titers against H3N2 (table 4). At 4 weeks, both cohorts failed to meet their respective CPMP seroprotection criteria for the H1N1 and B components (a primary failure). This study calculated and reported mean fold increase in HI antibody titers. Based on this, at both 4 and 20 weeks, seroconversion factor was satisfied for all components, by both cohorts. With respect to seroconversion rate, at 4 weeks, a 4-fold rise in GMTs relative to baseline for the H3N2, H1N1, and B components was reached by 91%, 42%, and 42% of the elderly, respectively; at 20 weeks, it was maintained for H3N2 (82%) but was at lower than the required CPMP seroconversion rate for the H1N1 (16%) and B (18%) components. Compared with that in the elderly, the rate of the 4-fold rise in GMTs against the H3N2 component in young adults was lower, but those against the H1N1 and B components were higher, at 4 weeks (82%, 54%, and 64%, respectively) and 20 weeks (71%, 43%, and 36%, respectively) (and, at 20 weeks in young adults, was also less than the CPMP requirement for the B component).

In previously unvaccinated elderly, Ruf et al. [34] reported that seroprotection rates, at 1 month after immunization, were >90% for all 3 components and that they still exceeded the CPMP criterion of 60% at ⩾8 months after vaccination. The Ruf et al. study reported seroconversion factor at 2 weeks postimmunization indicating >10-fold increase over baseline for all components; at month 8, GMTs still appeared more than 5-fold elevated over baseline (table 4).

In community-dwelling elderly, Praditsuwan et al. [35] reported no significant variation in seroprotection after influenza immunization based on age, nutritional status, or underlying chronic conditions. At 4, 20, and 52 weeks, seroprotection rates far exceeded the CPMP standard for the H3N2 and H1N1 components, but at no time point, initially or subsequently, were CPMP seroprotection rates met for the B component (a primary failure) (table 4).

In a final study, Hui et al. [36] reported seroprotective rates far exceeding, at both 4 and 24 weeks, CPMP standards for all vaccine components in community-dwelling elderly (table 4). GMTs against all 3 components were >2-fold above baseline at 4 and 24 weeks (table 4). A 4-fold rise in GMTs relative to baseline was observed, per CPMP specification, in >30% of the elderly cohort at 4 weeks, but not at 24

Table 4. Seroprotective rates and GMTs, by time since inactivated influenza immunization.

Time and/or cohort	H3N2 seroprotective rate, % (GMTs)	H1N1 seroprotective rate, % (GMTs)	B seroprotective rate, % (GMTs)
	MacKenzie (1977) [30]: 2 (16 μg) doses of subunit vaccine administered at 0 and 4 weeks, deep subcutaneously to young adults and elderly		
Baseline			
Young	19 (9)		
Elderly	14 (12)	NA	NA
4 weeks			
Young	NA (217)		
Elderly	NA (371)	NA	NA
7 weeks			
Young	NA (326)		
Elderly	NA (475)	NA	NA
30 weeks			
Young	71 (189)		
Elderly	71 (228)	NA	NA
50 weeks			
Young	55 (120)		
Elderly	57 (161)	NA	NA
	Brydak et al. (2003) [2]: 2 doses of split vaccine administered via unspecified route to young adults and elderly		
Baseline			
Young	0 (2)	0 (1)	0 (4)
Elderly	2 (3)	0 (2)	0 (2)
4 weeks			
Young	82 (116)	57 (44)	68 (50)
Elderly	91 (184)	42 (30)	42 (31)
20 weeks			
Young	71 (50)	43 (15)	36 (17)
Elderly	84 (73)	16 (7)	18 (7)
	Peters et al. (1988) [31]: 1 dose of split vaccine administered intramuscularly to elderly		
Baseline	62 (35)	12 (8)	36 (18)
4 weeks	93 (200)	57 (29)	81 (78)
20 weeks	79 (89)	37 (15)	63 (45)
	Delafuente et al. (1998) [32]: 1 dose of split vaccine administered intramuscularly to elderly		
Baseline	4 (~10)	85 (~55)	100 (~145)
6 weeks	54 (~30)	96 (~108)	100 (~270)
17 weeks	82 (~65)	100 (~100)	100 (~320)
	Buxton et al. (2001) [33]: 1 dose of split vaccine administered intramuscularly to elderly		
Baseline	~50 (38)	~45 (29)	~30 (26)
6 weeks	~80 (121)	~90 (141)	~82 (45)
12 weeks	~90 (182)	~85 (130)	~68% (43)
18 weeks	~95 (227)	~90 (131)	~68 (48)
24 weeks	92 (194)	80 (103)	56 (39)
	Ruf et al. (2004) [34]: 1 dose of split vaccine administered intramuscularly to elderly		
Baseline	34 (17)	24 (14)	29 (16)
4 weeks	90 (>100)	94 (>100)	91 (>100)
16 weeks	Reported >60 (~100)	Reported >60 (~100)	Reported >60 (~100)
32 weeks	Reported >60 (~90)	Reported >60 (~75)	Reported >60 (~75)

(continued)

Table 4. ***(Continued)***

Time and/or cohort	H3N2 seroprotective rate, % (GMTs)	H1N1 seroprotective rate, % (GMTs)	B seroprotective rate, % (GMTs)
	Praditsuwan et al. (2005) [35]: 1 dose of split vaccine administered intramuscularly to elderly		
Baseline	45 (NA)	39 (NA)	4 (NA)
4 weeks	99 (NA)	96 (NA)	48 (NA)
20 weeks	89 (NA)	95 (NA)	26 (NA)
52 weeks	81 (NA)	88 (NA)	16 (NA)
	Hui et al. (2006) [36]: 1 dose of split vaccine administered intramuscularly to elderly		
Baseline	84 (81)	42 (26)	98 (121)
4 weeks	98 (633)	86 (145)	100 (584)
24 weeks	100 (435)	79 (78)	100 (371)

NOTE. GMTs, geometric mean titers; NA, not available.

weeks, for the H3N2 component (47% and 30%, respectively), and at both time points the rise in GMTs was lower than CPMP specification for the H1N1 (25% and 13%) and B (17% and 12%) components.

In summary, CPMP seroprotection rates established for the annual approval of influenza vaccines in the elderly were maintained for >4 months by the elderly in all 8 of the studies of H3N2 and in 5 of the 7 studies of H1N1 and B. In all 8 of the studies of H3N2, in 5 of the 7 studies of H1N1, and in 3 of the 7 studies of influenza B, the higher CPMP seroprotection thresholds established for vaccine approval in young adults were also met by the elderly for >4 months (table 4 and figure 2*A*). Studies that reported failure of the elderly CPMP seroprotection criteria for >4 months for H1N1 and B components had failed initially 1 month after immunization (primary vs. secondary failure). If initially achieved after immunization, seroprotection rates of 70%–100% were then maintained not just at 4 months [32, 33] but also at 5 months [2, 31] and even at >6 months [30, 34–36] for the H3N2 and H1N1 components. For influenza B, seroprotective rates appeared to be less consistent throughout. In 1 of the 2 respective studies in which the H1N1 and B components failed the seroprotection criteria, these components would still have passed the CPMP guidelines at >4 months, on the basis of seroconversion criteria. A total of 4 studies compared antibody response by age, and no consistent differences were found [2, 30, 31, 35].

Studies reporting antibody results without providing seroprotective rates. Findings from 6 studies exploring antibody persistence without reporting seroprotective rates are described below in chronological order and in table 3 and figure 2*B*.

In young and elderly participants with comparable preimmunization titers, McElhaney et al. [37] reported no significant decline in GMTs between 6 and 24 weeks after receipt of a whole or split vaccine for the H3N2, H1N1, or B components in community-dwelling elderly—and they reported no differences in titers at 24 weeks, compared with the young adult group. At 6 weeks, increase in GMTs was satisfied in the young adult group (2.6-fold) for the split vaccine H3N2 component, but age-specific seroconversion factor did not appear to be met for any other split vaccine component for either the young or elderly at 6, 12, or 24 weeks. A 4-fold rise to any component was achieved in <30% of elderly and <40% of young adults initially after immunization (primary failure). Thus, from the results reported by McElhaney et al. and on the basis of seroconversion alone, this split vaccine would not have satisfied criteria even initially that year (figure 2*B*).

In community-dwelling elderly, Powers et al. [38] reported baseline titers against H1N1 that were ⩾32 in 100% of participants, reflecting their high rate of prior immunization (also see [29]) . Not surprisingly, all 100% still met the CPMP seroprotection criterion at 2–4 weeks after immunization. In that context, there can be little relevance to the poor vaccine performance initially conveyed through the seroconversion rate (<20% mounted a 4-fold rise in titers) or the seroconversion factor (GMTs before immunization, ~128, rose <2-fold, to 208, at 2–4 weeks after immunization, fell slightly, to 181, at 12 weeks, and returned to baseline, 128, by 18 weeks). Seroconversion was inversely correlated with preimmunization titers, but, unfortunately, seroprotection rates at >2–4 weeks, which would have provided added context, were not reported.

Van Hoecke et al. [39] assessed antibody response in an institutionalized population of elderly in the following age ranges: 65–80, 80–90, and 90–100 years of age. This study reported results for seroconversion factor at 4 weeks relative to baseline. The low preimmunization baseline GMTs were increased 7–8-fold for the H3N2 component and 4–5-fold for the H1N1 and B components at 4 weeks after immunization in all age groups. GMTs showed clear decline between 1 and 6 months after vaccination, but these were still >2-fold above baseline for all 3

A

Study & specific intervals	4–6 weeks			≥16 weeks		
	H3N2	H1N1	B	H3N2	H1N1	B
Mackenzie [30] (4, 30 weeks)	SF	Not reported	Not reported	SP[a]-SF	Not reported	Not reported
Peters et al. [31] (4, 20 weeks)	SP-SF	SP | SF	SP-SF	SP-SF	SP-SF	SP | SF
Delafuente et al. [32] (6, 17 weeks)	SP | SF	SP | SF	SP-SF	SP-SF	SP | SF	SP | SF
Buxton et al. [33] (single dose) (6, 18 weeks)	SP-SF	SP-SF	SP | SF	SP-SF	SP-SF	SP | SF
Brydak et al. [2] (4, 20 weeks)	SP-SF-SR	SP | SF-SR	SP | SF-SR	SP-SF-SR	SP | SF | SR	SP | SF | SR
Ruf et al. [34] (4, 32 weeks)	SP-SF	SP-SF	SP-SF	SP-SF	SP-SF	SP-SF
Praditsuwan et al. [35] (4, 20, 52 weeks)[b]	SP	SP	SP	SP	SP	SP
Hui et al. [36] (4, 24 weeks)	SP-SF-SR	SP-SF | SR	SP-SF | SR	SP-SF | SR	SP-SF | SR	SP-SF | SR

[a]Seroprotection rate reported at 30 weeks but not at 4 weeks postimmunization.

[b]Interpretation applies to seroprotection rates observed at all time intervals including 4, 20, and 52 weeks.

B

Study & specific intervals	4–6 weeks			≥16 weeks		
	H3N2	H1N1	B	H3N2	H1N1	B
McElhaney et al. [37] (6, 24 weeks)	SF-SR[a]	SF-SR[a]	SF-SR[a]	SF	SF	SF
Powers et al. [38] (4, 18 weeks)	Not reported	SP[a] | SF-SR[a]	Not reported	Not reported	SF	Not reported
Van Hoeke et al. [39] 65–80 years of age (4, 24 weeks)	SP[a]-SF-SR[a]	SP[a] | SF-SR[a]	SP[a]-SF-SR[a]	SF	SF	SF
Van Hoeke et al. [39] 80–90 years of age (4, 24 weeks)	SP[a] | SF-SR[a]	SP[a] | SF-SR[a]	SP[a]-SF-SR[a]	SF	SF	SF
Van Hoeke et al. [39] 90–100 years of age (4, 24 weeks)	SP[a]-SF-SR[a]	SP[a] | SF-SR[a]	SP[a]-SF-SR[a]	SF	SF	SF
Minutello et al. [40] Year 1: (4, 52 weeks)	SF-SR[a]	SF-SR[a]	SF-SR[a]	SF	SF	SF
Minutello et al. [40] Year 2: (4, 24 weeks)	SF-SR[a]	SF | SR[a]	SF | SR[a]	SF	SF	SF
Minutello et al. [40] Year 3: (4, 24 weeks)	SF-SR[a]	SF-SR[a]	SF-SR[a]	SF	SF	SF
Mysilwska et al. [41] Healthy, Year 1 (4, 20 weeks)	SF	SF	SF	SF	SF	SF
Mysilwska et al. [41] Healthy, Year 2 (4, 20 weeks)	SF	SF	SF	SF	SF	SF
Mysilwska et al. [41] Chronic, Year 1 (4, 20 weeks)	SF	SF	SF	SF	SF	SF
Mysilwska et al. [41] Chronic, Year 2 (4, 20 weeks)	SF	SF	SF	SF	SF	SF
Keylock et al. [42] High-fitness (6, 36 weeks)	SF	SF	SF	SF	SF	SF
Keylock et al. [42] Low-fitness (6, 36 weeks)	SF	SF	SF	SF	SF	SF

[a]Reported at 4–6 weeks but not ≥16 weeks postimmunization.

Figure 2. *A*, Studies reporting seroprotection rates. *B*, Studies reporting titers interpretable as seroconversion without reporting seroprotection rates. "Chronic" stands for elderly with chronic conditions. "Healthy" stands for healthy elderly. In both panels, the seroprotection rate (SP), seroconversion factor (SF), and seroconversion rate (SR) are provided as reported by a study among elderly participants and indicating vaccine components that would meet these Committee for Proprietary Medicinal Products (CPMP) criteria as specified for young adults *(no shading)* or older adults only *(light-gray shading)* or that would not meet *(dark-gray shading)* CPMP approval criteria for either age group at 4–6 or ⩾16 weeks postimmunization. For each study, meeting SP, SF, or SR for any component, as reported at each interval, implies that CPMP vaccine approval would be given at that interval for that component, based on young adult *(no shading)* or old adult *(light-gray shading)* CPMP criteria. Meeting SF was approximated on the basis of an *n*-fold increase in GMTs above baseline.

components at 6 months. Van Hoecke et al. reported no significant differences in the rate of antibody decline across any of the 3 age groups for any component, and results were unaffected by clinical status.

Minutello et al. [40] assessed antibody response in community-dwelling elderly immunized each year over 3 consecutive years. Preimmunization titers were higher during the second and third seasons. A >2-fold increase in GMTs against all 3 components was demonstrated at 1 month after immunization during the first 2 years (seroconversion factor). More than 30% also demonstrated a 4-fold rise for all 3 components at 1 month during the first year, for the H3N2 component alone during the second year, and for no component during the third year (seroconversion rate). At 1 month, during the third year of successive immunization, neither seroconversion criterion was met, for any component. Antibody persistence, determined on the basis of a 2-fold increase in GMTs relative to baseline, was not demonstrated in any study year for any component at 6 months (years 2 and 3) or 12 months (year 1).

In a study in which the first year overlaps with the study by Brydak et al. [2], Mysliwska et al. [41] reported the vaccine-induced antibody response over 2 seasons in semi-institutionalized (nursing home) elderly with and without chronic conditions. During both seasons, for all 3 vaccine components in both groups of elderly, GMTs were >2-fold elevated above baseline at 1 and 5 months after immunization, with the single exception of GMTs for influenza B in healthy elderly at 5 months after immunization in year 2 (figure 2*B*).

Finally, Keylock et al. [42] plotted post-immunization titers, up to 24 weeks, in community-dwelling elderly, with the intent of comparing immunogenicity among those deemed to have low versus high physical fitness. A high proportion (77% and 69%, respectively) of both the low- and high-fitness groups self-reported having received the previous season's influenza vaccine. Preimmunization titers were slightly higher in the low-fitness group. In the high-fitness group, titers >2-fold above baseline were evident for all components at 6 and 24 weeks; in the low-fitness group, a 2-fold rise above baseline was not apparent for any component at 4 or 24 weeks (a primary failure).

Two of these 6 studies compared antibody by age, and, in both, no consistent differences were found on the basis of age [37, 39]. In the other 4 studies [37, 38, 40, 42], the main reason for failure at 4 months was a primary failure at 1 month. Initial demonstration of seroconversion and its maintenance after immunization varied most substantially, and inversely, with preimmunization titers. In 2 of the 6 studies comparing antibody response by age, no consistent differences were found [37, 39].

DISCUSSION

For over a decade, advisory committees in North America have cautioned that antibody titers decline more rapidly in the elderly, falling below seroprotective levels within 4 months [11–14]. In the context of influenza activity that variably occurs over a 6-month winter period, this has led to difficulty in timing the immunization of elderly people so as to provide protection spanning the entire season without considering a second dose.

We identified 14 original studies that assessed antibody levels to ⩾4 months after split/subunit inactivated influenza immunization of elderly persons, and we presented results interpretable in the context of established vaccine-approval criteria. These studies include a wide variety of designs, sample sizes (mostly small), follow-up methods, and presentations of results with little individual detail to enable a pooled or quantitative summary or comparison; standardized collection, analysis, and presentation of immunogenicity data would be helpful. A large cohort study comparing young adults and elderly in terms of influenza vaccine–induced antibody response, slope of seasonal antibody decline, and rates of seroprotection, with adequate control for potential biases, is needed. Among the studies included in the present review, however, we could not find compelling evidence for rapid or meaningful same-season antibody decline in the elderly, either in general or in comparison with young adults.

A total of 6 studies included in the present review compared antibody persistence by age: 3 compared elderly with young adults [2, 30, 37], and 3 compared elderly by advancing age [31, 35, 39], with no consistent differences in antibody persistence found by age. In most studies, at the end of the season, the elderly still met the same age-specific CPMP criteria that had been used to approve vaccine for them at the start. CPMP seroprotection rates were met at >4 months after immunization, in almost all studies that assessed this. If initially achieved at 1 month after immunization, seroprotection rates in the range of 70%–100% for the H3N2 and H1N1 components were then also maintained for ⩾5–7 months. In a study that considered antibody levels as long as 1 year after immunization, seroprotection rates of >80% were maintained for these components after 1 dose [35]. Seroprotection rates appeared to be less consistent for influenza B. However, the relevance of a lesser response, as measured by an HI assay for this component, is unclear. Other studies have highlighted the relative insensitivity of the HI test for antibody against influenza B [8], as well as seroprotective thresholds that may be much lower than those for influenza A [4, 8]; in our experience, facility outbreaks due to influenza B or H1N1 are uncommon in institutionalized elderly, at any stage of the season. In the 6 studies that did not report seroprotection rates, we found more variability in satisfying the CPMP seroconversion criteria alone. In general, however, this could be traced to primary failure at the start of the season—often related to high preimmunization titers—rather than to secondary failure due to antibody decline.

Although we framed our interpretation of antibody persistence within the context of CPMP criteria specified for the elderly, the same interpretations would have been reached with regard to late-season vaccine approval, even if we had applied the higher thresholds specified for young adults (table 1 and figure 2*A* and 2*B*). There were just 2 exceptions to this, both for the influenza B component [33, 39].

In the studies included in the present review, antibody levels decreased with time from their initial postimmunization peak in both young adults and the elderly. The main issue, however, is the clinical relevance of that decline with respect to anticipated protection. In that context, in determining whether CPMP criteria were still met at season's end, primary antibody response in the elderly appeared to be more relevant than secondary antibody decline. Diminished primary antibody response to influenza vaccine in the elderly has been noted in some previous studies, whereas other studies have emphasized a response comparable to that in young adults [44, 45, 49–52]. In a review of 30 studies, Beyer et al. [50] found that primary antibody response to influenza vaccine was diminished with age in one-third of the studies and increased in 13%, with no difference based on age in 53% of the studies. In a more recent quantitative review based on publications between 1986 and 2002, Goodwin et al. [53] reported reduced primary antibody response to influenza vaccine in the elderly that also varied with influenza type/subtype (greater immunogenicity in association with H3N2, compared with H1N1 or B components). Both reviews highlighted methodologic flaws in studies of initial antibody response, including failure to exclude participants with conditions influencing the immune system, those previously vaccinated, or those with high prevaccination titers [50, 53]. In studies to assess the duration of antibody response, intercurrent influenza infection is an additional bias to consider. Eight studies in the present review addressed this either by excluding the cases of influenza from analysis or by reporting low rates of influenza infection that were unlikely to explain the observed antibody profiles. Immunogenicity interpretation overall then varied with the CPMP criterion selected for consideration: higher preimmunization titers were associated with a greater likelihood of showing seroprotection but with lower likelihood of demonstrating fold rises or seroconversion. In that regard, the present review, like other reviews, highlights the importance of including the seroprotection rate in the reporting of results [50, 54]. This indicator provides the more clinically relevant context, without which antibody response and persistence may be underestimated.

Despite attempts at standardization, serologic markers remain complex surrogates of vaccine efficacy that are difficult to compare across birth cohorts. Unlike most other pathogens, the influenza virus changes constantly. Intercohort differences in priming history with regard to one or another of the variants results in extreme heterogeneity in baseline influenza serology [37, 50, 54–59]. Initial priming experiences between young adults and the elderly differ markedly for H1N1 strains (circulating between 1918 and 1957 and reintroduced in 1976) but are more similar for H3N2 strains (circulating since 1968). When these differences are taken into account, the elderly appear capable of mounting and maintaining antibody responses similar to those observed in young adults with variations possibly attributed to priming experience rather than imaging of the immune system per se [37, 53, 56–59]. A stronger response to older versus recent H1N1 strains has been reported in the elderly, whereas higher titers to H3N2 strains can be generated in elderly, compared with younger persons, and can exceed that of H1N1 or B strains [37, 54, 56–59]. We found similar patterns, with the late-season antibody profile varying more with preimmunization titers, initial antibody response, and influenza subtype than with age.

Although we used CPMP criteria established for annual vaccine approval as the frame of reference to interpret antibody persistence, we recognize that these criteria, like other thresholds, are somewhat arbitrary, are subject to laboratory variation, and are not perfect correlates of protection [8, 59–62]. The elderly, in particular, remain at risk for influenza, despite vaccination and initial antibody response [1, 59, 63]. Conversely, those with lower titers may still be protected. Regulatory authorities are thus reexamining the validity and relevance of these serologic criteria, in their interpretation of both seasonal and pandemic vaccine performance. The importance of the cytotoxic T lymphocyte response in clearing virus from infected lung has been well established. Age-related declines in cell-mediated function, associated risks of serious illness, and their implications for vaccine performance in the elderly are increasingly recognized [65–69]. Efforts to standardize cell-mediated assays and to quantify the kinetics of that response are also warranted. For more than a decade, however, the cautionary statements of advisory committees regarding early loss of protection same-season in the elderly have been based only on antibody response. In that context, using the same CPMP serologic criteria as have been applied to annual vaccine approval at season's start to interpret antibody levels at season's end seems appropriate and even conservative.

In conclusion, we found no compelling evidence for more rapid decline of the influenza vaccine–induced antibody response in the elderly, compared with young adults, or evidence that seroprotection is lost at $\leqslant$4 months if it has been initially achieved after immunization. Given the implications for the timing of seasonal and pandemic influenza immunization programs, historic statements expressing these concerns should be reconsidered. It is worth noting that advisory committees in the United States and Canada have now dropped this emphasis

in their most recent 2007–2008 influenza statements [70, 71].

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