Reducing the impact of influenza on the elderly with high-dose influenza vaccine and other new vaccines

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Introduction:

The US Centers for Disease Control and Prevention estimates that over two thirds of influenza-related hospitalizations and nearly 90% of influenza-related deaths occur in those aged 65 years and older1,2 Remarkably, adults 65 years of age and older account for only about one in eight US residents.3 In order to mitigate the impact of influenza on the elderly, a high-dose, inactivated, split-virus influenza vaccine (IIV3-HD; Fluzone® High-Dose vaccine, Sanofi Pasteur) was developed.4 Should primary care practitioners routinely choose this vaccine for their elderly patients? This article highlights key issues that primary care practitioners should consider as they make this choice.

Rationale for a high-dose influenza vaccine for the elderly:

On the one hand, the elderly population, defined here as those 65 years of age or older, suffers from a disproportionate share of the impact of influenza, measured in hospitalizations and deaths. Yet this same segment of the population has, compared to other age groups, higher uptake of influenza vaccine.5 This seems paradoxical. However, an explanation is available from a multi-year study of standard-dose vaccine effectiveness.6 For those 15-64 years of age, vaccine effectiveness averaged about 70%; for older individuals, vaccine effectiveness was much less, averaging about 40%.
What is the basis for diminished vaccine effectiveness in the elderly? Part of the answer to this question comes from a series of studies that evaluated antibody responses in individuals who received influenza vaccine. Titers to the 2007-08 A/H1N1 strain in those aged 18 to 64 were four times as high as the titers in those 60 years and older. Another report contrasted titers in those aged 19 to 59 with older individuals. Titers among the older individuals were not even 50% of those in younger subjects.

The impact of lower hemagglutinin inhibition (HI) titers on the risk of influenza is evident. Several studies have clearly demonstrated that HI titers are inversely correlated with risk of influenza infection. The 2009 pandemic influenza strain was six times as likely to cause clinical illness in those with titers less than 1:8 in comparison with those with titers of at least 1:24. Various studies involved volunteers were immunized and subsequently challenged with exposure to influenza virus. These studies found infection rates over ten times as high in those with titers less than 1:6, compared to those with the highest titers in the experiments.

This literature suggests that a diminished response to influenza vaccine likely contributes to the increased burden of influenza in the elderly. A corollary is that this burden may be lessened through use of a vaccine that, compared to traditional influenza vaccines, induces higher antibody levels.

Standard-dose adult influenza vaccines for intramuscular injection contain 15 mcg of hemagglutinin (HA) antigen of each strain of influenza virus in the vaccine. High-dose vaccine contains 60 mcg of HA of each strain, which is four times as much HA content. A randomized, double-blind, controlled trial compared HI antibody levels achieved with standard-dose vaccine to those achieved with high-dose vaccine in the elderly. High-dose vaccine induced significantly higher levels of antibodies for all strains: A/H1N1, A/H3N2, and B. For example, the Day 28 geometric mean titer for A/H1N1 was 115.8 in the high-dose group but only 67.3 in the standard group. The increases in levels met criteria for statistical significance for all strains. The increases met prespecified superiority criteria for the A strains and the non-inferiority criteria for the B strain.

**Tolerability of high-dose vaccine:**

The observation that the high-dose vaccine provided more stimulation of the immune system, as measured by antibody responses, raises a question: Does the high-dose vaccine induce more local and systemic reactions? The investigators actively solicited reports of reactions, and in the high-dose group reactions were more common, albeit generally mild and transient.
The most common reaction was injection site pain, reported by 36% of the high-dose vaccine recipients and 24% of the standard-dose vaccine recipients. By day 4, injection site pain was reported by 3% and 2% respectively. Injection site erythema was reported by 15% of high-dose recipients and 11% of those receiving standard-dose vaccine. Swelling was the least common injection site reaction.

Overall, systemic reactions were reported by nearly the same proportion of recipients in each group, 34% of high-dose and 29% of standard-dose. Fever occurred in 4% of high-dose and in 2% of standard-dose. Headache occurred in 17% of high-dose and 14% of standard-dose. Malaise occurred in 18% of high-dose and 14% of standard-dose. Myalgia occurred in 21% of high-dose and 18% of standard-dose.

Unsolicited events were reported in 22% of each group.

**Efficacy of high-dose vaccine in a randomized, controlled trial:**

The data demonstrating lower risk of influenza infection among those with higher HI antibody levels, coupled with the finding of higher HI antibody levels in recipients of high-dose vaccine, generated an expectation: The high-dose vaccine would reduce the risk of laboratory-confirmed, clinical influenza. A randomized, double-blind, controlled trial\textsuperscript{13} tested this hypothesis. This 126-center trial was conducted in the 2011-12 and 2012-13 seasons among community-dwelling individuals 65 years of age and older in the United States and Canada. Participants were randomized 1:1 to the standard-dose trivalent vaccine or high-dose trivalent vaccine. Investigators actively sought influenza cases, contacting subjects at least once a week (twice weekly in January and February) and asking subjects to call in the event of respiratory symptoms.

The study randomized 15,998 subjects to standard dose (IIV3-SD) and 15,991 to high-dose (IIV3-HD). The standard-dose group had 301 cases of influenza (1.9%), but the number of cases was reduced 24.2% to 228 (1.4% of the subjects) in the high-dose group. 95% confidence intervals (CI) for the 24.2% reduction were 9.7% and 36.5%. An additional analysis, which was confined to cases of influenza (defined using a modified CDC case definition) caused by strains antigenically similar to those in the vaccine, found a more dramatic reduction of 51.1% (95% CI, 16.8% to 72.0%).

**Risk of serious adverse events with high-dose vaccine:**

The efficacy trial\textsuperscript{13} enrolled over ten times as many patients as did the earlier study of immunogenicity.\textsuperscript{12} The efficacy trial data were analyzed to address a concern: Does the high-dose vaccine pose an increased risk of serious, albeit uncommon, adverse events? During a six-month follow-up period in the immunogenicity trial,
serious events had occurred in 6% of the high-dose group and 7% of the standard group. In the efficacy trial, serious events occurred in 8.3% of the high-dose group and 9.0% of the standard-dose group. Additional analysis\(^\text{14}\) found that high-dose was associated with a 6.9% reduction in hospitalizations for any reason (95% CI, 0.5% to 12.8%) as well as a 17.7% reduction in serious cardio-respiratory events possibly related to influenza (95% CI, 6.6% to 27.4%). Perhaps most striking is the 39.8% (95% CI, 19.3% to 55.1%) reduction in serious pneumonia that was associated with the use of high-dose, compared to standard-dose.

The conclusion was that high-dose vaccine did not pose a risk of increasing serious adverse events; to the contrary, its reduction in hospitalizations made it, in this respect, more desirable than standard dose.

**Observational studies of high-dose vaccine effectiveness:**

In addition to studies of *efficacy* in a well-defined, closely observed set of enrollees in a randomized, controlled trial, studies of *effectiveness* can provide insight into the impact of a vaccine from observational data of relatively unselected populations.

The largest published observational study\(^\text{15}\) included Medicare beneficiaries who received influenza vaccine in the 2012-13 season. This included 929,730 who received high-dose and 1,615,545 who received standard dose. High-dose reduced non-hospital encounters for influenza 22% and hospital encounters also by 22%.

Investigators from the Veterans Health Administration (VA) reported a smaller study\(^\text{16}\) from the 2010-11 season. They included 25,714 high-dose recipients and 139,511 standard-dose recipients. They did not see a reduction in the risk ratio for hospitalization; the risk ratio of 0.98 had a 95% confidence interval of 0.68 to 1.40. However, the oldest Veterans (those 85 and older) had a reduction in the risk ratio to 0.52 (95% confidence interval, 0.29 to 0.92). The discrepancy between the Medicare and VA studies may reflect challenges in using a propensity score to reduce confounding, differences in racial composition of the study population, varying definitions of influenza-related hospitalization, different influenza seasons, and differing definitions of the duration of the influenza season.\(^\text{17,18}\)

Interestingly, other VA data—although analyzed in a simpler fashion—did detect benefit of high-dose vaccine in reducing the incidence of positive laboratory tests for influenza in both 2010-11\(^\text{19}\) and 2012-13.\(^\text{20}\)

Another large study of Medicare beneficiaries, contrasting those who received high-dose vaccine with those who received standard-dose vaccine, has been presented in abstract form.\(^\text{21}\) Averaged for two seasons, the reduction in influenza-associated death with high-dose was 24.0% (95% CI, 0.6% to 41.8%).
Cost-effectiveness of high-dose vaccine:

A mathematical model\(^{22}\) of the cost-effectiveness of trivalent high-dose vaccine (IIV3-HD), compared to standard-dose vaccine (IIV3-SD) looked at the impact that the high-dose vaccine was expected to have on the elderly in the US. Estimates included averting 195,958 cases of influenza, 22,567 hospitalizations, and 5,423 deaths. A gain of 29,023 Quality Adjusted Life Years (QALY) was expected at a cost of $5,299/QALY. Compared to quadrivalent standard-dose vaccine (IIV4-SD), trivalent high-dose vaccine yielded 27,718 more QALYs. High-dose was dominant in this cost-effectiveness analysis.

Instead of using a mathematical model, an additional study\(^{23}\) analyzed data from the efficacy trial\(^{13}\) to investigate the economic impact of high-dose vaccine. In the high-dose group, mean medical costs were $115.92 less (95% confidence interval, $264.18 less to $35.48 more) per participant. Of the savings, 95% reflected reduction in hospital costs. High-dose vaccine had a slight gain in QALYs (8.1502 vs. 8.1499) and dominated standard-dose vaccine in this cost-utility analysis.

In addition to those studies, whose lead author is an employee of the high-dose vaccine manufacturer, another cost-effectiveness study\(^{24}\) was funded by the National Institutes of Health. This study evaluated trivalent standard-dose vaccine (IIV3-SD), quadrivalent standard-dose vaccine (IIV4-SD), and trivalent high-dose vaccine (IIV3-HD). Compared to no vaccine, IIV3-SD cost $3,693 per QALY. Quadrivalent vaccine cost an additional $20,939 per QALY. Trivalent high-dose vaccine cost $31,214 more per QALY than did quadrivalent vaccine. The authors took into account an expectation that high-dose vaccine would produce 83,775 fewer cases and 980 fewer deaths than quadrivalent vaccine. They concluded that high-dose vaccine “is likely to be an economically favorable influenza vaccination strategy with a clear, moderate public health effect.”

High-dose vaccine as an alternative to quadrivalent or adjuvanted vaccine:

The NIH-funded cost-effectiveness study recognized, in addition to high-dose trivalent influenza vaccine (IIV3-HD) two other approaches to improving protection of the elderly from influenza by moving beyond standard trivalent vaccine (IIV3-SD): One approach was quadrivalent vaccine, which they included in their analysis. A second approach was adjuvanted vaccine; they mentioned the possibility of analyzing the impact of adjuvanted vaccine\(^{25}\) when more data become available.

The NIH-funded study estimated that quadrivalent vaccine (IIV4-SD) could, compared to standard trivalent vaccine (IIV3-SD), prevent 7.7% more influenza cases, hospitalizations, and deaths. The high-dose vaccine (IIV3-HD), compared to standard trivalent vaccine (IIV3-SD), was estimated to reduce cases, hospitalizations, and deaths by 24% (the effect on cases of illness seen in the efficacy trial).\(^{13}\) The limited benefit of the quadrivalent vaccine is a consequence of its principal difference from trivalent vaccine. The quadrivalent vaccine has an
additional B strain. This reduces the chance of a mismatch between the strain of influenza B used in the vaccine and the strain of influenza B that circulates. However, influenza B is generally more of a problem for children than for older adults. Thus, improved protection against influenza B has limited benefits for older adults.

The high-dose vaccine (IIV3-HD) improves antibody response through its increased antigen content. Another approach to improving antibody response is to administer a vaccine with an adjuvant. A review and meta-analysis of observational studies of the impact of the MF-59 adjuvanted vaccine on the elderly does represent an endorsement of the need for an improved vaccine for the elderly. That publication noted a paucity of studies, many with large confidence intervals, making it challenging to assess the effectiveness of MF59 trivalent inactivated vaccine.

**Conclusions:**

Compared to younger adults, those 65 years of age and older face a markedly increased risk of hospitalization and death from influenza. Part of the reason for this increased risk is likely due to the diminished antibody response to influenza immunization that is found in those with advanced age. This notion is supported by data showing that lower HI antibody titers are associated with increased risk of influenza infection. The trivalent high-dose influenza vaccine (IIV3-HD) induces higher antibody levels than standard-dose vaccine in the elderly. In a randomized, controlled, double-blind trial IIV3-HD reduced the risk of laboratory-confirmed, protocol-defined influenza illness by 24.2%. This effect was seen regardless of antigenic similarity between circulating influenza strains and the vaccine components. A similar reduction in influenza cases and influenza-related emergency department visits and hospitalizations was seen in a study of approximately 2.5 million Medicare beneficiaries. IIV3-HD does cause local pain in about one in eight patients who would not report pain with standard vaccine, but it is generally well tolerated. Owing to a reduction in hospitalizations, IIV3-HD recipients had fewer serious adverse events than standard vaccine recipients. Health economic evaluations concluded that IIV3-HD is cost-effective and may even be cost-saving and that, compared to standard-dose vaccine, it offers moderate public health benefit. For the elderly, it is preferable to quadrivalent vaccine (IIV4-SD). Data for another approach toward improving antibody response in the elderly, the MF-59 adjuvanted vaccine, are limited.
References:


