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Intranasal Cold-Adapted Influenza Virus Vaccine Combined with Inactivated Influenza Virus Vaccines

An Extra Boost for the Elderly?

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Abstract

Although influenza vaccine delivery strategies have improved coverage rates to unprecedented levels nationally among persons aged 65 years and older, influenza remains one of the greatest vaccine-preventable threats to public health among elderly in the US. A new, intranasal live attenuated influenza vaccine (LAIV) was recently approved by the US FDA for use in persons aged 5–49 years, which excludes the elderly population. Limitations of immune response to inactivated influenza vaccine (IAIV) and effectiveness of current influenza vaccination strategies among the elderly suggest that a combined approach using LAIV and/or the IAIV in various permutations might benefit this group. We explore characteristics of the LAIV, data regarding its utility in protecting against influenza in the elderly, and challenges and opportunities regarding potential combined inactivated/live attenuated vaccination strategies for the elderly. Although LAIV appears to hold promise either alone or in combination with IAIV, large well conducted randomised trials are necessary to define further the role of LAIV in preventing influenza morbidity and mortality among the elderly. We also suggest that innovative vaccine coverage strategies designed to optimise prevention and control of influenza and minimise viral transmission in the community must accompany, in parallel, the acquisition of clinical trials data to best combat morbidity and mortality from influenza.

The toll that influenza can exact annually from the US population is both tragic and staggering.[1-3] Every year, 20 000–40 000 deaths occur, up to 300 000 individuals require hospitalisation and countless others are temporarily unable to attend to their normal life activities. Furthermore, influenza disproportionately burdens children, the infirm and the elderly.[1] More than 90% of influenza and pneumonia deaths that occur during influenza epidemic periods are among persons aged 65 years or older.[4] Alarmingly, persons aged 85 years and older represent 1.5% of our current population, but will increase by almost 40% in the next 10 years and will

increase over 5-fold (to 19 352 000 persons) by the year 2050.[5-7]

Fortunately, there is a well tolerated and readily available inactivated influenza vaccine (IAIV) to augment the immune response against influenza and decrease the risk of acquiring or dying from this illness. Influenza vaccination-associated reductions in illness, hospitalisation and mortality among persons aged 65 years or older are well established and impressive, with decreases in influenza-related hospitalisation rates of 20–72% and mortality rates of 31–82% over a range of study designs and elderly populations.[8-14]

Unfortunately, not everyone is willing to receive the vaccine and not everyone responds immunologically to it. Vaccine responses in the elderly are frequently suboptimal, with an age-related attenuation of the immune response so that the elderly may not achieve adequate immunity against influenza infection and illness, especially when compared with responses seen in young healthy adults.[9,15] However, protection against influenza in the elderly can be improved. In June 2003, the US FDA licensed FluMist™ [1], an intranasally administered live attenuated influenza vaccine (LAIV) manufactured by MedImmune, Inc., Gaithersburg, MD, USA and Wyeth Pharmaceuticals, Collegeville, PA, USA for use in individuals aged 5–49 years.[16] Thus, it is provocative to consider opportunities to use LAIV alone or in combination with IAIV to improve prevention and control of influenza in the elderly.

1. Vaccine Formulations

The haemagglutinin and neuraminidase proteins on the virion surface are the primary antigens that stimulate an immune response to the influenza virus. For the purpose of this discussion, we will primarily focus on influenza A, which undergoes both major and minor genetic variations over time (shift and drift, respectively), while influenza B only appears to undergo drift.[17] The upper respiratory tract mucosa is the entry point of the influenza virus into the human body. Dimeric influenza-specific IgA secreted locally has been shown to be effective in inhibiting viral attachment and neutralising viral activation.[18] As such, many researchers have postulated that the first line of defence, mucosal or secretory IgA, may provide the best opportunity to prevent infection or blunt it early in its course, thus decreasing the severity of infection.

Serum antibody to the haemagglutinin glycoprotein is also responsible for viral neutralisation and resistance to infection, perhaps more so for the lower respiratory tract.[19] Once infected, the immune response to influenza relies on both cell-mediated and humoral immunity,[20] and although vaccination to induce humoral or systemic immunity is important in response to infection,[21] vaccination focused on humoral response alone may not provide full protection against infection.[22]

1.1 Inactivated Influenza Vaccine

IAIV, targeted at inducing systemic rather than local immunity, has been licensed in the US since the late 1950s[23] and has been routinely recommended since 1963.[24] Composed of whole virus or purified subunit antigens of the neuraminidase and haemagglutinin viral surface glycoproteins, the IAIV is administered intramuscularly.[1] Influenza vaccines currently contain two influenza A subtypes – H1N1 and H3N2, and influenza B. Antibodies to inactivated virus in vaccines can neutralise viral replication, but they may not induce adequate mucosal responses that minimise the risk of infection when administered intramuscularly.[25-27] Protection conferred by the vaccine has been shown to correlate directly with the immune response elicited in the recipient.[28] However, the strength of this association is not as clear in the elderly[29] and inactivated vaccines are predominantly only effective against viral strains that have similar haemagglutinin and neuraminidase antigens.[1]

1 The use of trade names is for product identification purposes only and does not imply endorsement.

1.2 Live Attenuated Influenza Vaccine (LAIV)

A live attenuated, cold-adapted vaccine has also been explored for over three decades in monovalent, bivalent and trivalent type A and B forms, and recent advances make this vaccine an option for the prevention and control of influenza. Cold adaptation of the vaccine virus was achieved through serial passage at successively lower temperatures, essentially restricting viral replication at 25–33°C and limiting it to the upper respiratory tract.[30,31] The vaccine is administered intranasally as a large-particle aerosol to the upper respiratory epithelium and is targeted at inducing an IgA response to the influenza virus. Although inactivated vaccines administered intramuscularly frequently produce higher titres of serum antibody to influenza virus, LAIV intranasally induces higher levels of secretory and local antibody.[32,33] One of the argued benefits of the LAIV is that the mucosal immune response to the live attenuated vaccine virus may more closely resemble a naturally occurring immune response than the response that is produced by inactivated vaccines.[34]

1.2.1 LAIV Safety

LAIV appears to be effective and have a good safety profile in randomised trials of children and healthy adults,[34-38] with no severe adverse reactions reported among adult participants in clinical trials, including the elderly.[39] In a trial of 5210 healthy subjects aged 1–65 years, the most common adverse reactions were sore throat, rhinorrhoea and headache.[40] Although the attenuated strain could theoretically recombine with a wild type variant and cause the potential for a novel viral pandemic, over 30 years of study have shown that the vaccine virus is genotypically stable and the theoretical reassortants that have been hypothesised have yet to be identified among any of the clinical trial participants to date.[41,42]

Some recipients shed detectable virus in nasal secretions for a short duration after vaccination. However, there has been only one abstract report of a placebo recipient acquiring an attenuated viral strain from an LAIV recipient in a Finnish clinical trial of children[43] and no other published studies have observed such transmission from vaccinated to unvaccinated persons.[44] Further discussions regarding the safety of the LAIV vaccine are reported in greater detail elsewhere.[45,46]

2. Vaccine Response in the Elderly

Maximising or augmenting immunity is particularly desirable for elderly vaccinees. Not only are IAIV humoral and cellular immune responses thought to be diminished with respect to the magnitude of response in the elderly, but the time it takes to obtain protection and persistence of adequate response to maintain protection are thought to be diminished as well.[47-51] In mouse models, diminished efficacy of the inactivated vaccine among elderly mice is thought to reflect immune senescence,[52] although not all studies in humans have demonstrated lower post-vaccination antibody titres among the elderly when compared with younger subjects.[53]

Among 127 nursing home residents aged 60–98 years who were vaccinated with trivalent IAIV, 25% remained unprotected against influenza 1 month post-vaccination with haemagglutinin inhibition titres <1 : 40.[54] This titre is considered the standard for demonstration of response to vaccination,[55] although a positive response at 1 : 40 may not necessarily be protective against influenza infection or other clinically relevant outcomes. Blunted responses are not confined to institutionalised elderly with multiple comorbidities. Bernstein et al.[56] observed that after administration of a trivalent IAIV to a group of 233 healthy community-dwelling elderly, only 48.9% and 30% had persistent humoral and cell-mediated immune responses to any of the three vaccine strains, respectively, 1 month after vaccination. The apparently lower response among healthy elderly persons relative to those in nursing homes is counterintuitive, but may reflect differences in prior exposure, in history of repeat annual

influenza vaccination,[57] or in pre-vaccination antibody levels to influenza antigens.

Hoskins et al.[58] originally suggested that repeated annual influenza vaccinations may decrease the protective response over time, although a meta-analysis examining the differences in clinical and serologic outcomes between first-time influenza vaccinees and those having repeated annual vaccination suggested no evidence for a worse outcome in the latter group.[57,59] Ahmed et al.[60] demonstrated a 75% reduction in mortality among elderly persons who had received multiple annual influenza vaccinations versus a 9% reduction for first-time vaccinees, although the study lacked sufficient power for the mortality difference to reach statistical significance. Betts et al.[61] reported that among persons receiving IAIV, admission serum influenza antibody levels were lower in those who were hospitalised for pneumonia (mean 1 : 26) than in those who did not develop pneumonia (mean 1 : 48). High antibody titres (1 : 256 or above) in this study were also associated with a significantly lower risk of influenza detection in respiratory secretions from participants. However, the validity of any absolute age insensitive standard for antibody response to inactivated vaccination may be questionable, as responses that would confer protection in younger persons do not necessarily provide adequate immunity from infection in the elderly. For example, in a study comparing trivalent IAIV with a diphtheria toxoid conjugated vaccine containing the same antigens, 60% of elderly nursing home residents who developed laboratory-confirmed influenza infection had serum antibody titres 1 : 40 or above 1 month after vaccination.[62]

Both young and elderly adults with mucosal rather than parenteral administration of inactivated vaccine[25,57,63-66] tend to exhibit greater increases in secretory IgA levels. Elicitation of significantly increased mucosal IgA as a result of vaccination with intranasal whole IAIV has been demonstrated in multiple studies.[64-66] In a study of 92 subjects aged 55 years and older, Muszkat et al.[57] observed that among participants receiving inactivated intranasal vaccination, 49.8–52.5% attained a positive nasal response (a positive response was defined as a 1.4-fold increase in nasal antibody levels, or titre of 1 : 40 or above in serum antibody levels) to H1N1, H3N2 and B antigens, and 27.1–37.1% attained a positive serum response to those antigens. Among participants receiving intramuscular IAIV, 19.4–25.8% attained a positive nasal response and 41.9–58.1% attained a positive serum response to H1N1, H3N2 and B antigens. Lower humoral responses to intranasal versus intramuscularly administered inactivated vaccine have also been consistently observed in other observational and experimental settings.[25,38,63-65]

Similarly, the extent of the immune response to LAIV, as measured by post-vaccination serum or secretory immunoglobulin titres, does not appear as vigorous among the elderly as in children or young adults. In a small study (n = 34) comparing antibody response to monovalent LAIV in young and elderly healthy adults with pre-vaccination serum haemagglutination inhibition (HAI) antibody titres ≤1 : 8, Powers et al.[67] found that while 100% of young adults developed a response to the vaccine, only 36% of elderly persons developed a response (95% CI 17, 61%). However, local IgA responses may be seen in >60% of elderly recipients of LAIV vaccine,[68] and LAIV appears to provide greater stimulation of local immunity when compared directly with inactivated vaccine among the elderly. For example, Gorse et al.[69] used monovalent LAIV in a small sample (n = 48) of elderly adults with chronic diseases and observed that 88% demonstrated an immune response to the vaccine virus. When compared with elderly subjects administered IAIV intramuscularly, similar rates of serum antibody response were observed between the two groups. Those receiving LAIV more frequently demonstrated a nasal IgA response, but the study lacked sufficient statistical power for the difference between the two groups to reach statistical significance.

In a trial of bivalent LAIV among male chronic obstructive pulmonary disease patients aged 42–88 years who received intramuscular IAIV, Gorse et al.[70] showed that participants who received both vaccines had significantly higher levels of mean anti-haemagglutinin (HA) antibodies in intranasal washings than those with IAIV alone who had no increase relative to pre-vaccination levels. Only one patient had shedding of vaccine virus up to 7 days after vaccination, and the virus retained its cold-sensitive phenotype. Both groups exhibited a similar but moderate proportion of participants with a 4-fold increase in serum anti-HA antibodies (from 46% to 63%) and all had higher serum titres 21–28 days post-vaccination compared with 7–10 days post-vaccination. However, this does not confirm that the local immune response is always better with LAIV than inactivated vaccines among the elderly. In several studies, there were no differences in mucosal antibody response to either LAIV or intramuscularly administered IAIV, although these studies had smaller samples sizes.[65,66,68] Furthermore, the variable use of monovalent, bivalent and trivalent LAIV in these studies complicates extrapolation of results to the currently available trivalent LAIV.

3. Vaccine Efficacy

Immune response and efficacy are well correlated for IAIV in children and young adults, but not in the elderly. In healthy young adults, inactivated vaccine efficacy against illness reaches 70–90% when the antigens chosen for the vaccine match those of the epidemic strain.[71] In the elderly, the protection appears to be much lower, although lack of standardisation with respect to clinical outcomes between studies often makes age-related comparisons difficult. In an investigation by Falsey et al.,[72] over 200 elderly persons hospitalised with culture positive influenza were examined for vaccine status and 61% had received IAIV that year. These data are consistent with that observed in the Medicare Demonstration Project (Rochester, NY, USA), in which 58.2% of culture-positive elderly who were hospitalised for influenza received IAIV,[61] but both observations are limited by lack of morbidity and mortality rates in a comparison nonvaccinated group. Community-dwelling elderly persons who were enrolled in an urban health maintenance organisation who received IAIV had statistically significant 27–39% reductions in annual hospitalisation for acute and chronic respiratory conditions, as well as 48–57% reductions in hospitalisations specifically for influenza and pneumonia compared with nonvaccinees.[9] It is also notable that pre-vaccination comorbidity was greater among vaccine recipients in this study, which could lead to an underestimation of vaccine efficacy.

In a meta-analysis conducted in the mid-1990s, Gross et al.,[15] found that the pooled estimates of IAIV efficacy for 20 cohort studies in the elderly were as follows: 56% for preventing respiratory illness, 53% for preventing pneumonia, 48% for preventing hospitalisation and 68% for preventing death. A more recent study focusing on elderly residents of 83 Michigan, USA nursing homes estimated a pooled vaccine effectiveness of only 33.1% for the prevention of total respiratory illness.[73] Although a lack of standardised definitions for influenza-related conditions and health outcomes interferes with precise estimation of true IAIV efficacy, only a single study examined favoured no vaccination, and results from this study were statistically insignificant.[74] It is also notable that because other respiratory pathogens can cause acute illness during influenza season, studies may tend to underestimate vaccine efficacy and overestimate case-fatality rates.[75-79]

Despite variations in local IgA and serum antibody responses between LAIV and IAIV, it appears that efficacy against culture-confirmed influenza A infections is equivalent.[40] In a meta-analysis of 19 studies (all before 1996 and only five of which specifically focused on the elderly), IAIV and LAIV were observed to have similar frequencies of systemic reactions and similar efficacy for preventing culture-positive influenza illness. Importantly,

match or mismatch with epidemic strain, age of vaccinees, and study design did not differentially affect overall results observed between vaccines.[38]

Regardless, there have still been no large randomised clinical trials directly comparing the efficacy of LAIV and IAIV in the elderly. Initial recommendations in 1963 by the Advisory Committee on Immunisation Practices for the use of IAIV in the elderly were based on findings in young adults.[80] Ethical considerations for withholding IAIV in randomised controlled trials prevented subsequent collection of data on vaccine efficacy in the elderly in the US.[81] Thus, it was not until 30 years later that a large, double-blind, placebo-controlled trial undertaken in The Netherlands and examining the efficacy of influenza vaccination in the elderly was reported[8] and corroborated retrospective opinion regarding the benefit of influenza vaccination in the elderly. Rather than assuming that LAIV will confer the same benefits as it appears to in the younger population or restrict its use to a supplemental immunoprophylactic agent, large, well conducted clinical trials need to be undertaken in a scientifically rigorous manner to provide sufficient evidence to answer the question comparing IAIV and LAIV efficacy for influenza prevention and control in the elderly.

4. Combined Inactivated and Live Intranasal Vaccination Strategies

4.1 Efficacy

Whether both vaccines administered together could provide an extra protective boost to the elderly is a related and important question. This question was asked in a randomised, double-blind, placebo-controlled trial by Treanor et al.[39] that compared a regimen of LAIV plus IAIV to IAIV alone among 523 nursing home elderly. Decreases in both influenza-like illness and culture-positive influenza A infection were observed among recipients of both vaccines. Statistically significant increases in vaccine efficacy for preventing laboratory documented influenza A and outbreak-associated influenza-like illness (61% and 65%, respectively) were found for recipients of both vaccines relative to those who received IAIV alone. Moreover, the relative decrease in influenza attack rates among recipients of both vaccines was highest among persons with the lowest levels of pre-vaccination antibody titres in a re-analysis of the original data.[82] The latter point is consistent with past observations suggesting that the greatest benefit may exist for those with limited previous exposure or inability to maintain immune status, and may suggest that additional data on the sequencing of vaccinations are necessary to determine an optimal regimen for a combined vaccination strategy. Conceivably, programmatic permutations, such as utilising the same or different seasonal antigens in IAIV and LAIV formulations (to potentially broaden coverage)[83] with simultaneous or staggered dates of administration, might lead to variations in overall protection against influenza. Treanor et al.[39] began to address the potential benefits of a two-vaccine strategy for influenza prevention and control, but these and other significant questions regarding efficacy still need to be resolved before such an approach could be considered feasible and beneficial.

4.2 Target Populations

In addition to addressing the relative efficacy of LAIV in the elderly, prospective clinical trials may provide valuable information regarding populations in whom the vaccine may confer added benefit, such as those with specific conditions or multiple comorbidities. This information could guide future trials aimed at the elderly population[12,84] and optimise definition of the target populations for potential combination LAIV/IAIV strategies.

4.3 Cost Effectiveness

Establishing efficacy and the appropriate populations for vaccination are also critical to understanding the cost effectiveness of the vaccination programmes. The cost-benefit of IAIV strategies in the

elderly are well established,[85] but the cost effectiveness of LAIV in the elderly is unknown. For example, LAIV is more expensive than IAIV and requires storage at −15°C rather than refrigeration.[46] Among other routine adult vaccines, only varicella vaccine requires frozen storage,[86] therefore vaccination programmes employing IAIV and LAIV vaccines may require acquisition of additional space and facilities to store both vaccine types. Other cost-related questions arise regarding decisions to utilise the same or different antigens in IAIV and LAIV formulations, as well as simultaneous or staggered administration of vaccine doses. For feasibility reasons, simultaneous administration would be preferred. All of these issues could significantly impact the general usefulness of combined vaccination strategies, and cost-effective implementation of influenza control employing LAIV must be thoughtfully developed for combined IAIV/LAIV vaccine strategies to be successful.

5. Vaccine Coverage

Critical to any discussion of improving prevention and control of influenza in the elderly is improved vaccination coverage, regardless of the type or number of vaccinations provided.[87] In 1999, 66.9% of persons aged 64 years and older who responded to the US Behavioral Risk Factor Surveillance System indicated that they had received an influenza vaccination in the previous year.[88] The Healthy People 2010 coverage target is 90% of persons aged 65 years and older.[89] Bratzler et al.[90] found that in 1998, only 2.6% of fee-for-service Medicare patients aged 65 years and older who were hospitalised and had been previously unvaccinated received influenza vaccination during their hospitalisation. Low compliance with recommended annual inactivated vaccination against influenza in the elderly is a clear limitation of current vaccination programmes.[91]

The addition of the LAIV formulation could complicate guideline adherence further if elderly patients begin to refuse the more invasive IAIV in lieu of the LAIV formulation only (which is currently not approved for patients aged 50 years or older), potentially resulting in lower overall coverage or diminished efficacy. Inadequate vaccine coverage among the elderly deleteriously affects both individual protection and herd immunity, and it is unclear how partial immunisation with IAIV or LAIV might lead to complications in establishing herd immunity or increasing risks of potential viral reassortants in the community.

The elderly also appear to benefit from influenza vaccination coverage of children. Studies of the time-course of influenza epidemics observe that morbidity and mortality among the elderly occur following peak morbidity in the general community, which in turn appears to follow peak morbidity among children. These lags, which comprise a time span of weeks, suggest that children may represent the primary vector for viral transmission.[92,93] As such, intensive efforts focused on vaccination of children may decrease morbidity and mortality among the elderly.[94] However, annual intramuscular vaccination of children is a daunting prospect from a practical public health point of view, and makes intranasal formulations more appealing for this purpose. In fact, this is the age group for which commercial intranasal formulations are now being readied.

Potter et al.[95] demonstrated that vaccination of healthcare workers in geriatric long-term-care hospitals resulted in a significant reduction in patient mortality and occurrence of influenza-like illness, even in settings where patients were not routinely vaccinated. This study is relevant because healthcare workers often do not adhere to recommendations for influenza vaccination, with only about 38% receiving vaccinations in the year 2000 according to data from the National Health Interview Survey.[96] A recent cost-benefit analysis of influenza vaccination among healthy adults suggested that there may be a population-level benefit to the vaccination of adults aged 18–50 years who work in the healthcare industry.[97] Although this was an economic analysis

focused primarily on symptom relief and lost workdays due to influenza, significant benefits were predicted for vaccination versus nonvaccination of this group in almost all cases examined. Extending the observation that influenza morbidity and mortality rates in the elderly temporally follow that of the general community, an argument could be made for even greater population-level direct and indirect benefits for annual vaccination of healthy adults. Although previous studies[98-100] corroborate the results observed in the studies by Potter et al.[95] and Lee et al.[97] concerning the economic benefits of vaccinating healthy adults both within and outside the healthcare industry, not all cost-effectiveness studies have reached the same conclusions[101,102] and variations in methodological approaches, populations studied and definitions of outcomes call for additional well conducted trials to address this topic. Improving adherence to current influenza vaccination guidelines or expanding adult recommendations for LAIV or IAIV usage may provide additional opportunities for improving influenza prevention and control with or without undertaking combination vaccination strategies in the elderly.

6. Conclusion

LAIV appears to be well tolerated and have a good safety profile, and able to induce a protective immune response. However, efficacy studies of LAIV in the elderly have, to date, been limited by small sample sizes, attention to immune function and response parameters that have incomplete correlation with clinical outcomes and lack of direct comparison to IAIV for clinical outcomes of practical interest. Despite these caveats, the available information suggests that LAIV and combined LAIV/IAIV vaccination strategies merit further scientific consideration.

In order to appropriately answer questions regarding the potential benefits of LAIV, either alone or in combination with IAIV, for influenza prevention and control in the elderly, large well conducted clinical trials specific to the elderly are necessary to ideally define efficacy of LAIV relative to and in combination with IAIV. Other issues requiring clearer evidence for use of a combined vaccine strategy include potential targeting of high-risk elderly populations, whether different HA and NA subtypes can be used between the IAIV and LAIV vaccines for serial or parallel administration to broaden immunity against more influenza strains within a given season[83] and whether repeat annual vaccination with LAIV eventually results in persistent immunity that prevents effective uptake and replication of the live attenuated vaccine virus in the host.[45] The optimal period between vaccinations in a combined strategy and the practical barriers to successfully and cost effectively implementing these strategies also need to be addressed. Finally, regardless of the vaccine or vaccines best supported for use by the evidence, innovative vaccine coverage strategies must be developed to attain the Healthy People 2010 targets of influenza prevention and control in the elderly.

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