

Debate Continues Over Flu Vaccine Strategies

BY KATE JOHNSON
Montreal Bureau

The benefits of vaccinating the elderly population against influenza may be substantially less than previously thought, and concentrating immunization efforts on the younger population with high-risk conditions might result in better outcomes, according to two separate studies.

Alternatively, funneling the limited vac-

cine supply to school-aged children could result in indirect community-wide protection, another group suggests.

Although the Centers for Disease Control and Prevention's Advisory Committee on Immunization Practices (ACIP) is currently finalizing new vaccination guidelines based on three tiers of priority (see related story on p. 1), debate continues among researchers worldwide over the best way to use the limited vaccine supply.

Vaccinating the Elderly

Even as ACIP's proposed new guidelines place the elderly population in the first tier of vaccination priorities, a study from the National Institutes of Health (NIH) challenges the assumption that vaccinating this population results in decreased influenza-related mortality (Arch. Intern. Med. 2005;165:265-72).

Increased vaccination rates among the elderly population (aged 65 and older) since before 1980 should theoretically have substantially decreased pneumonia and influenza mortality rates in this age group, reported Lone Simonsen, Ph.D., an epidemiologist at the NIH, and colleagues.

But the authors documented no change in the number of deaths attributable to influenza. They used a cyclical regression model to generate estimates of national influenza-related mortality for 33 influenza seasons between 1968 and 2001, adjusting for the increase in average age of the elderly population over this time period, as well as for the increased frequency of influenza A-dominant seasons in the 1990s.

"Our findings indicate that the mortality benefits of influenza vaccination may be substantially less than previously thought," they reported.

This difference between their findings and those of observational studies attributing as much as a 50% reduction in deaths among the elderly to influenza vaccination may be partly explained by a "hypothesis of disparity in vaccination: Very ill elderly people, whose fragile health would make them highly likely to die over the coming winter months, are less likely to be vaccinated during the autumn vaccination period," they noted. Thus, some or all of the reduction in mortality observed in some of these studies was "not attributable to vaccination, but rather to underlying differences between vaccinated and unvaccinated cohorts," they suggested.

Keiji Fukuda, M.D., an epidemiologist at the CDC, said the new study will not change ACIP's three-tiered priority guidelines for vaccination. The study's ability to draw conclusions about vaccination's effectiveness is "quite limited," because it did not directly compare illness and death in vaccinated and unvaccinated people.

The authors "did not say that vaccine doesn't work," he told this newspaper. "Based on these considerations, both CDC and NIH strongly believe that vaccination of the elderly must continue, even while we try to develop better ways to protect this most fragile and vulnerable of groups."

Vaccinating the Old and the Young

In contrast with the NIH study, a separate study published in the same issue of the journal documented substantial benefits to vaccinating both elderly people as well as younger individuals who are at high risk of complications from influenza (Arch. Intern. Med. 2005;165:274-80).

This case-control study nested within the larger Dutch Prevention of Influenza, Surveillance, and Management (PRISMA) study included 8,593 subjects, reported Eelko Hak, Ph.D., of University Medical Center Utrecht, the Netherlands, and colleagues.

The subjects were grouped into three categories: high-risk children and adolescents aged 6 months to 17 years; high-risk adults aged 18-64 years; and people aged 65 years and older.

The study was conducted during the 1999-2000 influenza A epidemic and the two following influenza seasons, in which influenza activity was very mild.

Under Dutch guidelines, high-risk medical conditions include chronic bronchitis, emphysema, asthma, and other respiratory diseases; acute or chronic ischemic heart disease, heart failure, atrial fibrillation, and other heart disease; cerebrovascular disease; diabetes mellitus; chronic renal disease; chronic staphylococcal infection; and immune-related diseases.

Among the 411 high-risk children and adolescents, 58% (240) had been vaccinated against influenza, as had 70% of the 1,778 high-risk adults (1,246), and 81% of the 6,404 elderly people (5,197).

The study identified 1,920 patients who experienced 2,095 episodes of influenza. There were 320 deaths, 192 hospitalizations, and 1,583 GP visits.

Using incidence rates among unvaccinated subjects during the 1999-2000 influenza A epidemic and adjusting for age, gender, comorbidities, and health insurance coverage, the authors calculated the protective effect of vaccination in the cohort.

They found that among high-risk children, vaccination prevented 43% of GP visits for influenza, pneumonia, acute exacerbations of chronic lung disease, and acute otitis media.

Additionally, vaccination prevented 78% of deaths, 87% of hospitalizations, and 26% of GP visits among high-risk adults. And among elderly subjects, vaccination prevented 50% of deaths and 48% of hospitalizations.

"The results of our study lend strong support for the view that all high-risk persons benefit from annual influenza vaccination, regardless of age," the authors said.

Vaccinating Children

But with such low vaccination rates in high-risk populations, vaccination strategies should be reconsidered, according to a commentary published in a separate journal (Am. J. Epidemiol. 2005;161:303-6).

Targeting school-aged children—the group most responsible for community-wide transmission—while maintaining immunization in high-risk and elderly individuals could greatly curtail the spread of influenza in the general population, according to Ira M. Longini Jr., Ph.D., and M. Elizabeth Halloran, M.D., of Emory University in Atlanta.

Mathematical models and evidence from community trials suggest that by vaccinating school-aged children, transmission can be reduced in the entire community, they reported.

"The best strategy for minimizing the number of influenza deaths and morbidity ... would be to concentrate vaccine in the high-risk and high-transmitting population groups simultaneously," they said. This could be achieved by targeting 70% of schoolchildren, as well as high-risk groups.

and a one-year study of once weekly FOSAMAX[®] (alendronate sodium) 70 mg) the rates of discontinuation of therapy due to any clinical adverse experience were 2.7% for FOSAMAX 10 mg/day vs. 10.5% for placebo, and 6.4% for once weekly FOSAMAX 70 mg vs. 8.6% for placebo. The adverse experiences considered by the investigators as possibly, probably, or definitely drug related in ≥2% of patients treated with either FOSAMAX or placebo are presented in the following table.

	Osteoporosis Studies in Men Adverse Experiences Considered Possibly, Probably, or Definitely Drug Related by the Investigators and Reported in ≥2% of Patients			
	Two-year Study		One-year Study	
	FOSAMAX 10 mg/day % (n=146)	Placebo % (n=95)	Once Weekly FOSAMAX 70 mg % (n=109)	Placebo % (n=58)
Gastrointestinal				
acid regurgitation	4.1	3.2	0.0	0.0
flatulence	4.1	1.1	0.0	0.0
gastroesophageal reflux disease	0.7	3.2	2.8	0.0
dyspepsia	3.4	0.0	2.8	1.7
diarrhea	1.4	1.1	2.8	0.0
abdominal pain	2.1	1.1	0.9	3.4
nausea	2.1	0.0	0.0	0.0

Prevention of osteoporosis in postmenopausal women

The safety of FOSAMAX tablets 5 mg/day in postmenopausal women 40-60 years of age has been evaluated in three double-blind, placebo-controlled studies involving over 1,400 patients randomized to receive FOSAMAX for either two or three years. In these studies the overall safety profiles of FOSAMAX 5 mg/day and placebo were similar. Discontinuation of therapy due to any clinical adverse experience occurred in 7.5% of 642 patients treated with FOSAMAX 5 mg/day and 5.7% of 648 patients treated with placebo.

In a one-year, double-blind, multicenter study, the overall safety and tolerability profiles of once weekly FOSAMAX 35 mg and FOSAMAX 5 mg daily were similar.

The adverse experiences from these studies considered by the investigators as possibly, probably, or definitely drug related in ≥1% of patients treated with either once weekly FOSAMAX 35 mg, FOSAMAX 5 mg/day or placebo are presented in the following table.

	Osteoporosis Prevention Studies in Postmenopausal Women Adverse Experiences Considered Possibly, Probably, or Definitely Drug Related by the Investigators and Reported in ≥1% of Patients			
	Two/Three-Year Studies		One-Year Study	
	FOSAMAX 5 mg/day % (n=642)	Placebo % (n=648)	FOSAMAX 5 mg/day % (n=361)	Once Weekly FOSAMAX 35 mg % (n=362)
Gastrointestinal				
dyspepsia	1.9	1.4	2.2	1.7
abdominal pain	1.7	3.4	4.2	2.2
acid regurgitation	1.4	2.5	4.2	4.7
nausea	1.4	1.4	2.5	1.4
diarrhea	1.1	1.7	1.1	0.6
constipation	0.9	0.5	1.7	0.3
abdominal distention	0.2	0.3	1.4	1.1
Musculoskeletal				
musculoskeletal (bone, muscle or joint) pain	0.8	0.9	1.9	2.2

Concomitant use with estrogen/hormone replacement therapy

In two studies (of one and two years' duration) of postmenopausal osteoporotic women (total: n=853), the safety and tolerability profile of combined treatment with FOSAMAX 10 mg once daily and estrogen ± progestin (n=354) was consistent with those of the individual treatments.

Treatment of glucocorticoid-induced osteoporosis

In two, one-year, placebo-controlled, double-blind, multicenter studies in patients receiving glucocorticoid treatment, the overall safety and tolerability profiles of FOSAMAX 5 and 10 mg/day were generally similar to that of placebo. The adverse experiences considered by the investigators as possibly, probably, or definitely drug related in ≥1% of patients treated with either FOSAMAX 10 mg/day (n=157), FOSAMAX 5 mg/day (n=161), or placebo (n=159), respectively, were: **Gastrointestinal:** abdominal pain (3.2%; 1.9%; 0.0%), acid regurgitation (2.5%; 1.9%; 1.3%), constipation (1.3%; 0.6%; 0.0%), melena (1.3%; 0.0%; 0.0%), nausea (0.6%; 1.2%; 0.6%), diarrhea (0.0%; 0.0%; 1.3%); **Nervous System/Psychiatric:** headache (0.6%; 0.0%; 1.3%).

The overall safety and tolerability profile in the glucocorticoid-induced osteoporosis population that continued therapy for the second year of the studies (FOSAMAX: n=147) was consistent with that observed in the first year.

Paget's disease of bone

In clinical studies (osteoporosis and Paget's disease), adverse experiences reported in 175 patients taking FOSAMAX 40 mg/day for 3-12 months were similar to those in postmenopausal women treated with FOSAMAX 10 mg/day. However, there was an apparent increased incidence of upper gastrointestinal adverse experiences in patients taking FOSAMAX 40 mg/day (17.7% FOSAMAX vs. 10.2% placebo). One case of esophagitis and two cases of gastritis resulted in discontinuation of treatment.

Additionally, musculoskeletal (bone, muscle or joint) pain, which has been described in patients with Paget's disease treated with other bisphosphonates, was considered by the investigators as possibly, probably, or definitely drug related in approximately 6% of patients treated with FOSAMAX 40 mg/day versus approximately 1% of patients treated with placebo, but rarely resulted in discontinuation of therapy.

Discontinuation of therapy due to any clinical adverse experience occurred in 6.4% of patients with Paget's disease treated with FOSAMAX 40 mg/day and 2.4% of patients treated with placebo.

Laboratory Test Findings

In double-blind, multicenter, controlled studies, asymptomatic, mild, and transient decreases in serum calcium and phosphate were observed in approximately 18% and 10%, respectively, of patients taking FOSAMAX versus approximately 12% and 3% of those taking placebo. However, the incidences of decreases in serum calcium to <8.0 mg/dL (2.0 mM) and serum phosphate to <2.0 mg/dL (0.65 mM) were similar in both treatment groups.

Post-Marketing Experience

The following adverse reactions have been reported in post-marketing use:

Body as a Whole: hypersensitivity reactions including urticaria and rarely angioedema. Transient symptoms of myalgia, malaise and rarely, fever have been reported with FOSAMAX, typically in association with initiation of treatment. Rarely, symptomatic hypocalcemia has occurred, generally in association with predisposing conditions.

Gastrointestinal: esophagitis, esophageal erosions, esophageal ulcers, rarely esophageal stricture or perforation, and oropharyngeal ulceration. Gastric or duodenal ulcers, some severe and with complications have also been reported (see WARNINGS, PRECAUTIONS, Information for Patients, and DOSAGE AND ADMINISTRATION).

Skin: rash (occasionally with photosensitivity), pruritus, rarely severe skin reactions, including Stevens-Johnson syndrome and toxic epidermal necrolysis.

Special Senses: rarely uveitis, rarely scleritis.

For more detailed information, please read the complete Prescribing Information.

FOSAMAX is a registered trademark of Merck & Co., Inc.



© 2004 Merck & Co., Inc., Whitehouse Station, NJ 08889, USA. All rights reserved.

20406286(1)(025)-FOS