The Silver Bullet of Perioperative Risk Assessment?


Karthikeyan G, Moncur RA, et al.::
J Am Coll Cardiol 2009; 54 (October 20): 1599-1606

Preoperative brain natriuretic peptide levels are an independent predictor of cardiovascular complications after non-cardiac surgery.

**Background:** Clinical predictors of perioperative cardiac events are of only modest utility. While imaging studies are of use in further refining perioperative risk, they are expensive and may not be sufficiently cost-effective. There is a need for a quick, inexpensive test that can be used to predict cardiac events in the 30 days following non-cardiac surgery.

**Objective:** To evaluate the predictive value of brain natriuretic peptide (BNP) in cardiac risk assessment of non-cardiac surgery.

**Design:** Meta-analysis to answer this question: Is BNP or N-terminal pro–B-type natriuretic peptide (NT-proBNP) an independent predictor of cardiac complications within 30 days of non-cardiac surgery?

**Methods:** An intensive search for articles and abstracts was performed that included preoperative assessments of either BNP or NT-proBNP with perioperative cardiovascular complications including death, cardiovascular death, all forms of acute coronary syndrome (ACS) including myocardial infarction (MI), coronary revascularization, arrhythmias requiring treatment including cardiac arrest, congestive heart failure, or rehospitalization due to a cardiac cause. Studies were excluded if they did not have a preoperative BNP, did not report BNP as solely a continuous variable but also included a threshold value, or did not have detailed 30-day outcomes.

**Results:** Of 564 references, 529 were excluded after preliminary screening, and ultimately 9 studies fulfilled criteria for inclusion, all of which were prospective cohort studies. Usual meta-analysis assessment for study quality was performed. Among studies, average age of participants ranged from 57 to 74 years, there was a large number of vascular surgeries, and BNP/NT-proBNP threshold levels varied widely (BNP, 40 to 189 pg/mL, and NT-proBNP, 201 to 533), and a specific threshold was not identified. Only 1 study included emergency surgery; all others were elective. Of 3281 patients, 314 experienced perioperative cardiac complications. All studies reported that BNP was an independent predictor of outcomes, including 3 that included left ventricular ejection fraction measurements. Preoperative BNP elevation was an independent predictor of cardiovascular events at 30 days. Data from the pooled analysis excluded 1 study that used atrial fibrillation as an outcome, and another with a loose definition of ACS. The pooled analysis had an odds ratio (OR) of 19.3 (95% CI, 8.5 to 43.7), while the OR for studies that included only death, cardiovascular death, and MI was higher at 44.2 (95% CI, 7.6 to 257.0).

**Conclusions:** Preoperative BNP is a powerful predictor of cardiovascular events within 30 days after non-cardiac surgery. This may provide an inexpensive, rapid means of preoperative assessment of cardiovascular risk.

**Reviewer’s Comments:** This interesting meta-analysis clearly demonstrates that BNP levels beyond a threshold are strong predictors of perioperative outcomes. However, the threshold used in each study is so variable as to preclude extrapolation to a specific value based on the meta-analysis. An adequately powered prospective study is ongoing that should have sufficient data and detail to allow application to clinical practice.

Additional Keywords: None

Print Tag: Refer to original journal article
Smoking laws are effective in a rapid and sustained decline in community rates of acute myocardial infarction.

**Background:** Passive smoking is associated with an increased risk of myocardial infarction (MI), and studies have shown a significant decrease in MI after implementation of public smoking bans in Europe and North America. The magnitude of the decrease varies in studies, but it is greater than the described rate of disease associated with second-hand smoke (SHS).

**Objective:** To update current data regarding the magnitude of decrease in MI following implementation of laws making public places smoke-free.

**Methods:** This study used a simple random-effects meta-analysis as well as a meta-regression, focusing on reduction in MI risk as a function of time following implementation of public smoking bans. Nine studies and 3 presentations at meetings were included; all reported the experience of laws banning smoking in public places in specific communities. Some studies used reported cotinine concentrations before and after smoking bans. Community rates of acute MI were estimated as a function of the distribution of individual relative risks, which incorporated current active and passive smoking exposure, the prevalence of active and passive smoking, quitting smoking because of restrictive laws, and lower SHS exposure for those who continue to have SHS after enactment of restrictive laws. Several equations and models were generated. A simulation estimating the ratio of community rates of acute MI after enactment of restrictive laws divided by community rates before enactment was performed for 48 different combinations of parameters.

**Results:** A random-effects model was used due to significant heterogeneity, likely resulting from differing end points, confounding variables considered, analytical methods, changing SHS exposure, and duration of follow-up. Analysis showed 76% of variance was accounted for by duration of follow-up. After adjustments, the different studies had consistent reductions in acute MI rates, with exponential declines as time passed following implementation of laws. There was an approximate 15% drop in acute MI rates in the first year after law implementation and an approximate 36% drop at 3 years.

**Conclusions:** The variability in reported studies of the impact of smoking laws is largely due to variable follow-up periods. This analysis demonstrates an immediate and sustained benefit of smoking laws that increases with time.

**Reviewer’s Comments:** This is a complicated study from a mathematical and statistical perspective, but it does succeed in accounting for some of the variability across different studies of the effect of smoking laws on acute MI rates. It adds weight to the argument that passive smoking is a significant public health hazard, and laws banning smoking in public places are effective in decreasing rates of acute MI.

Additional Keywords: None

Print Tag: Refer to original journal article
Does Defibrillator Placement Early After MI Help?

Defibrillator Implantation Early After Myocardial Infarction.
Steinbeck G, Andresen D, et al.: 

In patients with acute myocardial infarction, early implantation of an implantable cardioverter-defibrillator in those at increased risk does not improve mortality.

**Background:** Implantable cardioverter-defibrillator (ICD) placement has been shown to be beneficial in some patients with ischemic cardiomyopathy. However, current recommendations require that at least 40 days have passed since time of myocardial infarction (MI). As much of the mortality associated with survivors of MI is days to weeks after the primary event, there has been interest in whether early ICD placement may be beneficial.

**Objective:** The Immediate Risk Stratification Improves Survival (IRIS) trial sought to determine if early implantation of an ICD in patients with MI and increased risk for death would decrease mortality.

**Design:** Multicenter, randomized, prospective open-label trial.

**Participants:** Patients presenting with acute MI with 1 of 2 criteria: (1) decreased left ventricular ejection fraction (LVEF; ≤40%) and heart rate ≥90 beats/minute on admission ECG; or (2) presence of non-sustained ventricular tachycardia (NSVT) on Holter monitoring (on days 5 to 31). Exclusions included ventricular arrhythmias requiring treatment and class IV heart failure.

**Methods:** Within each group, patients were randomized to ICD or not. The primary outcome was overall mortality. Secondary outcomes included rates of sudden and non-sudden cardiac death.

**Results:** Of nearly 63,000 patients screened, 898 were ultimately enrolled; 602 for the first criterion of decreased LVEF, 208 with the second criterion of NSVT, and 88 with both. After a mean follow-up of 37 months, the overall mortality rate was 26%. Rates were nearly identical between the ICD group and the control group (116 deaths in patients with an ICD and 117 in controls). In looking at each of the predefined criterion groups, ICD therapy did not improve overall mortality. Sudden cardiac death did occur less frequently in the ICD group (27 vs 60; \( P = 0.049 \)), but non-sudden cardiac death occurred more frequently (68 vs 39; \( P = 0.001 \)). In the group receiving an ICD, 16% had significant complications (requiring hospitalization, surgery, or IV drug administration).

**Conclusions:** In patients with acute MI, early implantation of an ICD in those at increased risk does not improve mortality.

**Reviewer’s Comments:** The period shortly after MI has always been a high-risk time. However, in the era of improved management, patients are doing reasonably well (as shown by the 12% mortality in the control group at 1 year). Clearly, aggressive management is making a big difference. From this study, it does not appear that adding ICD to such treatment confers any net benefit. The reasons behind the increased non-sudden cardiac death seen with ICD therapy are not entirely clear. Perhaps this is related to issues around placement of the ICD. For now, we should continue to treat these patients aggressively, but wait at least 40 days before considering an ICD in selected patients with a decreased LVEF.

Additional Keywords: None

Print Tag: Refer to original journal article
In patients with decreased left ventricular function and prolonged QRS complex, addition of cardiac resynchronization therapy to implantable cardioverter-defibrillator placement decreases the frequency of heart failure events.

**Background:** Implantable cardioverter-defibrillators (ICDs) have been shown to improve outcomes, including survival, in patients with decreased ejection fraction (EF). However, long-term ICD therapy has been associated with increased heart failure episodes. Cardiac resynchronization therapy (CRT) with biventricular pacing is beneficial in patients with symptomatic heart failure, an EF ≤35%, and evidence of cardiac dyssynchrony (QRS interval of ≥120 msec).

**Objective:** To look at patients with minimally symptomatic heart failure, depressed left ventricular function, and prolonged QRS and to test whether the addition of CRT to ICD therapy would decrease deaths and heart failure episodes as compared to ICD alone.

**Participants:** Patients aged ≥21 years with an EF of ≤30%, NYHA class I or II heart failure (for non-ischemic, only class II), and QRS duration of ≥130 msec were eligible.

**Methods:** Patients were randomized in a 3:2 ratio to receive an ICD-CRT or ICD alone. The primary end point was any-cause death or heart failure events. Heart failure was diagnosed by clinicians who were aware of study group assignment but were adjudicated by a blinded heart failure committee. The trial was stopped early when pre-determined end points were reached.

**Results:** 1820 patients were enrolled and followed up for an average of 2.4 years. The primary end point occurred in 17.2% of patients (187 of 1089) with ICD-CRT and 25.3% (185 of 731) in the ICD-only group. As rates of death were similar in both groups (approximately 3%), this finding was due to reduced heart failure events in the ICD-CRT group. This was similar in both ischemic and non-ischemic cardiomyopathy patients. Complication rates were low in both groups.

**Conclusions:** In patients with decreased left ventricular function and prolonged QRS complex, the addition of CRT to ICD placement decreases the frequency of heart failure events.

**Reviewer's Comments:** As I attempt to medically manage my patients with heart failure, I have not consistently considered the role of referral for ICD and CRT. This study is a good reminder. First, it reminds me of recommendations for ICD treatment in patients with decreased LV function. As well, it points out that CRT may be useful for other patients instead of only patients with progressive heart failure symptoms. It is important to note that this was not a blinded study, and that overall mortality was not affected. However, if a device is to be placed, perhaps the addition of CRT may help decrease rates of heart failure exacerbations.

Additional Keywords: None

Print Tag: Refer to original journal article
Psyllium Better Than Bran for IBS Symptoms

Soluble or Insoluble Fibre in Irritable Bowel Syndrome in Primary Care? Randomised Placebo Controlled Trial.
Bijkerk CJ, de Wit NJ, et al.:
BMJ 2009; 339 (August 27): b3154

Psyllium appears to be more effective than bran in reducing symptoms in patients with irritable bowel syndrome.

Background: Irritable bowel syndrome (IBS) is common, with a prevalence of approximately 10%, and treatment is challenging. Most primary care physicians recommend increasing fiber intake, often in the form of insoluble fiber (bran). The degree to which fiber (both soluble and insoluble) is effective for IBS symptoms is unclear.

Objective: To determine the effectiveness of soluble and insoluble fiber on symptoms and quality of life in patients with IBS.

Design: Randomized placebo-controlled trial, blinded to patients and study authors.

Participants: Patients in the Netherlands aged 18 to 65 years with a prior diagnosis of IBS (within 2 years) or with a new diagnosis (during the study) were invited to participate. Inclusion criteria were symptoms within the last 4 weeks with either "definite" IBS according to Rome II criteria or "probable" IBS as diagnosed by their primary care physician. Exclusion criteria were other organic bowel disease, fiber treatment within the last 4 weeks, or specialist treatment for IBS in the prior 2 years.

Methods: Patients were randomized to 10 g psyllium (soluble), 10 g bran (insoluble), or 10 g rice flour (placebo) for 12 weeks. Primary outcome was response to "did you have adequate relief of IBS symptoms in the past week?"; secondary outcomes were symptom severity, abdominal pain, and quality of life, each assessed by questionnaire after 1, 2, and 3 months of treatment.

Results: 275 patients were randomized (94% white; 78% female; mean age, 34.4 years). During the trial, approximately 40% of patients dropped out of the study (similar in each arm), mostly for "feeling worse" on treatment. In the intention-to-treat analysis, response (>2 weeks of adequate symptom relief per month) was significantly higher for psyllium than for placebo at 1 month (57% vs 35%; relative risk [RR], 1.6; number needed to treat [NNT], 4.0) and at 2 months (59% vs 41%; RR, 1.44; NNT, 5.9) but not at 3 months. Psyllium appeared most effective in patients whose symptoms fit Rome II criteria. In the third month, bran appeared more effective than placebo (57% vs 32%; RR, 1.7). Severity of symptoms was also improved at month 3 in the psyllium arm. Adverse events were similar across groups (mostly constipation and/or diarrhea).

Conclusions: Psyllium (rather than bran) appears to be an effective treatment approach in patients with IBS.

Reviewer's Comments: This nice trial shows that psyllium is probably superior to bran for control of IBS symptoms. Patients who self-select into this kind of study may be different (more intense abdominal pain, more consultations, etc) than all-comers with IBS, and once the study was ongoing, many folks dropped out. Thus, the results aren't completely generalizable and may be overconfident. Furthermore, this is a short study of only 3 months, and researchers were unable to show symptom improvement beyond 1 and 2 months. However, treatment with psyllium is safe, fairly inexpensive, and seems worth a try in our IBS patients.

Additional Keywords: None

Print Tag: Refer to original journal article
Disease-Modifying Treatment for Parkinson?

A Double-Blind, Delayed-Start Trial of Rasagiline in Parkinson's Disease.

Olanow CW, Rascol O, et al:.

In early Parkinson disease, rasagiline at a dose of 1 mg daily (and not 2 mg) slows the progression of disease, but the clinical significance remains unclear.

**Background:** Rasagiline, a monoamine oxidase type B inhibitor, has shown promise in potentially modifying progression of Parkinson disease (PD).

**Objective:** To determine if use of rasagiline early in the course of PD can modify progression.

**Design:** Randomized, double-blind placebo-controlled trial with a delayed start design. In this design, patients are randomized to either drug or placebo for an initial phase, and then all patients receive drug for the second phase.

**Participants:** Patients aged 30 to 80 years with PD who were not receiving treatment were eligible.

**Methods:** Patients were randomized to rasagiline (either 1 or 2 mg daily) for 72 weeks (early start group) or placebo for the first 36 weeks followed by rasagiline at either dose for the following 36 weeks (delayed start group). The primary outcome was a complicated one, requiring that 3 separate criteria be met (based on the Unified Parkinson's Disease Rating Scale, a 176-point scale with a higher score indicating more severe disease). The criteria were that, between weeks 12 and 36, the rate of clinical change needed to favor medication over placebo. The early start group also had to show better clinical scores than the delayed group at study completion. Lastly, the rate of change during weeks 48 and 72 (when all groups were on rasagiline) could not be inferior for the early start group.

**Results:** 1176 patients were enrolled, with an average age of 62 years and 4 to 5 months since time of diagnosis. In the rasagiline 1-mg group, all 3 components of the primary outcome were met, indicating some degree of disease modification. However, in the rasagiline 2-mg group, as the net change in scores was similar at 72 weeks for both groups, the end point was not met.

**Conclusions:** In early PD, rasagiline at a dose of 1 mg daily (and not 2 mg) slowed progression of disease, but the clinical significance remains unclear.

**Reviewer's Comments:** This is a confusing study. First, whenever a trial uses a scale that is not used regularly by clinicians, it is difficult to determine the clinical significance of changes reported. I'm not certain of the relevance of the 2.8- vs 4.5-point difference seen at 72 weeks for the early start vs late start groups. As well, it is not clear why the primary end point was met with the 1-mg dose but not the 2-mg dose. The authors spend considerable effort discussing this, but it is obviously concerning. Therefore, at this point, it appears that rasagiline 1 mg might slow the rate of disease, but the clinical importance of this remains unclear.

Additional Keywords: None

Print Tag: Refer to original journal article
Objective: To present an exhaustive and critical review of the literature on methotrexate treatment of rheumatoid arthritis (RA), and to attempt to identify the optimum dose and route of administration of methotrexate in RA patients to optimize response and minimize toxicity.

Methods: Approximately 50 papers were reviewed and compiled on the subject, describing 38 randomized controlled trials: 30 evaluating methotrexate as monotherapy and 8 comparing oral methotrexate in differing doses and route of administration.

Results: The results strongly support reaching high weekly doses (25 to 30 mg/week) of methotrexate in a short period, but toxicity was a limiting factor. The mean tolerable effective dose in these studies was 17 to 20 mg/week; however, 2 studies did not use folic acid supplementation to minimize side effects, which could skew the results. Parenteral methotrexate, either subcutaneous or intramuscular injection, allows for greater bioavailability with increasing dose. The difference in bioavailability is demonstrated by equivalent effects obtained with oral methotrexate at doses that were 2.5 to 5.0 mg/week higher than parenteral doses producing the same effect. There was a decrease in gastrointestinal side effects noted when methotrexate was given parenterally. Despite a 3-day half-life of the active form of methotrexate, a twice-weekly dosing schedule showed no benefit over once-a-week dosing. Some patients in remission on weekly methotrexate were able to maintain their remission when switched to every-other-week dosing, but remission was not maintained in all patients.

Reviewer's Comments: This article recommends starting methotrexate in RA patients at a dose of 15 mg/week orally and increasing by 5 mg/week each month to 25 to 30 mg/week or the highest dose tolerated. Folic acid supplementation can help reduce the incidence of side effects when given along with methotrexate. For those patients in whom remission is not achieved on this regimen, switching to a parenteral route of administration can recapture remission in some patients, without increasing the frequency of gastrointestinal side effects.
Topical treatment with diclofenac gel helps reduce pain in patients with hand osteoarthritis.

**Objective:** To assess the safety and effectiveness of diclofenac sodium gel in patients with primary hand osteoarthritis (OA).

**Design:** Randomized, double-blinded placebo-controlled trial.

**Participants:** The study population included 385 patients aged >40 years with symptomatic OA in their dominant hands and who had definite x-ray changes. Participants had to have used NSAIDs for at least 1 pain episode in the past, have significantly more pain in the dominant hand than the non-dominant hand, and to have endured a washout phase prior to trial beginning.

**Methods:** Acetaminophen, up to 4 g/day, was allowed during the study period of 8 weeks on an as-needed basis. Of patients, 198 used diclofenac gel 4 times a day to affected areas, and 187 used the vehicle alone in the same manner for the entire 8-week study period. Evaluation at 4, 6, and 8 weeks included OA pain intensity score and the Australian/Canadian Osteoarthritis Hand Index (AUSCAN) score, which is a measure of pain, stiffness, and function, as well as use of rescue medication and global rating of disease activity.

**Results:** Overall, the treatment group experienced a reduction in pain intensity, AUSCAN score, and global disease activity of around 40% at 4 and 6 weeks. Withdrawals from the study occurred early, and most were related to excessive use of rescue medication in the first few weeks. Adverse events were noted in 52.0% of treatment the group and 43.9% of the placebo group (mainly headache and skin irritation). Mild gastrointestinal symptoms were noted in 7.6% of the treatment group and 3.7% of the placebo group.

**Reviewer's Comments:** A nice industry-sponsored trial of topical treatment for hand OA. Study participants were vigilant about applying the medication topically 4 times a day and maintaining this for the whole 8 weeks. Improvement in function occurred with pain relief. Adverse events were frequent but mild. Topical diclofenac gel is a useful treatment for pain relief in hand OA, especially in patients who cannot tolerate NSAIDs and pain medication.

Additional Keywords: None

Print Tag: Refer to original journal article
Potassium citrate therapy was shown to be effective in reducing the risk for recurrence of kidney stones. Favorable changes in urinary metabolic profiles persisted over 40 months of follow-up.

**Background:** Potassium citrate (KCit) therapy is often used therapeutically for patients with a history of recurrent calcium oxalate or mixed calcium kidney stones; citrate therapy is particularly helpful in patients with absolute or relative hypocitraturia, a common risk factor for nephrolithiasis. While previous studies have demonstrated short-term efficacy of KCit in reducing the incidence of recurrent stones, no study has evaluated long-term consequences of KCit therapy.

**Objective:** To evaluate long-term consequences of KCit therapy in patients with a history of recurrent nephrolithiasis.

**Methods:** The study was performed at a nephrolithiasis specialty clinic at a single institution. The authors identified a cohort of patients who had multiple urinary metabolic evaluations between 2000 and 2006. Among this cohort, a little more than half had been treated with KCit for at least 6 months. A subset of patients was selected for analysis of the incidence of stone formation by careful review of patient history and follow-up radiographic imaging.

**Results:** 503 patients with multiple urinary metabolic profiles were included in the study; of these, 269 were treated with KCit for at least 6 months. Patients had an average of 2.4 metabolic abnormalities on initial metabolic profile, most commonly hypocitraturia (75%), low urine volume (61%), hypercalciuria (45%), and gouty diathesis (40%). Patients treated with KCit were treated for an average of 40.6 months (range, 6 to 168 months). KCit therapy had a number of significant durable effects on metabolic profiles. Urine pH, urinary citrate, and urinary potassium were all significantly increased ($P < 0.001$).

**Conclusions:** KCit therapy resulted in long-lasting changes in metabolic profiles and a reduction in the rate of recurrent stone formation.

**Reviewer's Comments:** This study confirms the long-term efficacy of, KCit therapy, which is commonly used to treat recurrent calcium oxalate or mixed calcium stones. The authors demonstrated durable changes in metabolic profiles for patients treated with KCit; these metabolic profiles were associated with a reduction in the rate of formation of recurrent stones. Several features of the study are worth noting. The study was done at a referral center, so the generalizability is uncertain. The cohort was assembled post hoc from patients who returned to the clinic on multiple occasions, so it may be biased toward patients who had a positive response to therapy. Finally, stone formation rate depended on patient recall and review of imaging studies, so it may not be accurate. Nonetheless, this study provides evidence for durable benefit from a commonly used therapy.
Hyponatremia is associated with an increased risk for mortality, even when the hyponatremia is mild. The increased risk for mortality can persist for up to 5 years.

**Background:** Hyponatremia affects up to 30% of hospitalized patients, making it the most commonly found electrolyte abnormality. It has been previously reported that the risk of death is increased by >50% among patients with hyponatremia compared with normonatremia, although it is not known whether the magnitude of risk correlates with severity of hyponatremia.

**Objective:** To study the short- and long-term mortality of a cohort of >95,000 inpatients with hyponatremia.

**Participants/Methods:** The study population consisted of patients who were admitted during the 3 years between January 2000 and December 2002 and had at least 1 sodium measurement. The authors obtained the following data from the hospital database: demographics, length of stay, vital status (for up to 5 years post-discharge), ICD-9 discharge diagnoses (up to 12 per patient), diagnosis-related group (DRG), and inpatient sodium and glucose measures. The relationship between mortality, sodium concentration, and other patient variables was explored through logistic regression.

**Results:** The study population consisted of 98,411 patients, among which hyponatremia was present in 14,290 (14.5%) on admission and developed during hospitalization in an additional 5093 (total of 19.7%). Corrected for hyperglycemia using 3 different formulas, the percent of patients with hyponatremia varied between 16.0 and 17.4. The majority of patients with hyponatremia had mild cases (130 to 134 mEq/L), and only 0.2% were severe.

**Conclusions:** Hyponatremia was associated with an increased risk for in-hospital, 1-year, and 5-year mortality.

**Reviewer's Comments:** There were several particularly interesting aspects to this study: (1) about 12.1% of patients with hyponatremia were actually normonatremic or hypernatremic when corrected for hyperglycemia; (2) the increased risk of mortality associated with hyponatremia extended to at least 5 years following hospital discharge; and (3) the increased risk of hyponatremia was present even in patients with mild hyponatremia. Interestingly, hyponatremia was not associated with mortality for a number of important medical disorders, including sepsis, pneumonia, or respiratory disease. While it is not surprising that hyponatremia was associated with mortality in patients with cardiac disease or metastatic cancer, the association with orthopedic surgery bears further study.
Facemasks, Hand Hygiene Limit Seasonal Influenza Transmission at Home

Facemasks and Hand Hygiene to Prevent Influenza Transmission in Households: A Cluster Randomized Trial.

Cowling BJ, Chan K-H, et al::

Ann Intern Med 2009; 151 (October 6): 437-446

In real-life conditions, facemasks and hand hygiene instructions given within 36 hours of an influenza-infected person’s symptoms onset significantly reduces the infection rate among household contacts.

**Objective:** To assess the efficacy of hand hygiene and facemasks in preventing influenza transmission in the home.

**Design:** Randomized controlled trial of households.

**Participants:** 794 household contacts (from 259 Hong Kong households) of patients with symptoms of influenza and a positive rapid test for influenza A or B, subsequently confirmed with polymerase chain reaction (PCR) testing.

**Methods:** Each household was randomized to 1 of 3 groups: control, enhanced hand hygiene, and hand hygiene plus facemasks. Within 2 days of randomization, and ideally within 12 hours, each household received a home visit. Control households were taught about healthy diet and lifestyle. Hand hygiene households, including the index patient, received soap and alcohol hand gels and instructions for using them. The facemask group, including the index patient, received facemasks and instructions to wear them as much as possible for 7 days, in addition to the hand hygiene intervention. All household members were asked to keep symptom diaries. Nasal and throat swabs were done at baseline and at 3 and 6 days, regardless of clinical illness.

**Results:** Overall, 8% of household contacts developed PCR-confirmed influenza. The risk was higher for households where a child was the index case, and children had a higher rate of secondary infection than did adults. Overall, the risk of influenza was similar in the 3 intervention groups. In 154 households in which the intervention was made within 36 hours of the index patient's symptom onset, however, the risk of household transmission was substantially lower with facemasks plus hand hygiene (odds ratio, 0.33). The overall adherence to facemask use was low, with about half the index patients and fewer contacts reporting they used one.

**Conclusions:** Despite incomplete adherence, facemasks and hand hygiene, when implemented early after onset of symptoms, reduced the rate of household transmission of seasonal influenza.

**Reviewer’s Comments:** It certainly makes sense that early intervention as soon as symptoms begin is more effective than later intervention, as this study showed. The general public should be aware that enhanced hand hygiene, both for the index patient and family members, should start as soon as symptoms do. The relative contribution that early hand hygiene and facemasks made wasn't clear in this study.

Additional Keywords: None

Print Tag: Refer to original journal article
Live vs Inactivated Flu Vaccine -- Does It Matter?

Comparative Efficacy of Inactivated and Live Attenuated Influenza Vaccines.

Monto AS, Ohmit SE, et al::

The intramuscular inactivated influenza vaccine appears significantly more effective than the intranasal live attenuated vaccine in preventing influenza A in healthy, young adults.

**Background:** The nasally inhaled attenuated live influenza vaccine is not approved in adults aged >50 years. Although approved for younger, healthy adults, few data exist comparing vaccination options.

**Objective:** To assess the efficacy of both inactivated and attenuated live vaccines in healthy adults aged

**Design:** Randomized, double-blind placebo-controlled trial.

**Participants:** Adults aged 18 to 49 years were recruited at sites in Michigan in the fall of 2007. People were excluded if they had any contraindication to either vaccination.

**Methods:** Subjects were randomized to receive intranasal live attenuated vaccine, intranasal placebo, intramuscular (IM) inactivated vaccine, or IM placebo in a 5:1:5:1 ratio. They recorded any reactions for 7 days after receiving their intervention. They were asked to report if they developed ≥2 respiratory or systemic symptoms over the following flu season. If symptoms did develop, pharyngeal swabs were obtained to identify those with influenza, using either viral culture or polymerase chain reaction.

**Results:** 1952 participants were recruited, with an average age of 23 years. Roughly 37% had received the influenza vaccination in the past. In those receiving IM injection, arm soreness was more common in those who received the vaccine compared to those who received placebo (53% vs 21%). As for the intranasal version, more participants receiving the vaccine complained of runny nose or congestion compared to those who received placebo (52% vs 38%). No significant severe adverse events related to vaccination were reported. There were 119 participants (6.1%) diagnosed with influenza over that season: 91% with influenza A and 9% with influenza B. Circulating strains of influenza A were similar to that in the vaccines. Subjects who received vaccination were significantly less likely to be diagnosed with influenza: 3.4% with inactivated injection, 6.9% with live attenuated intranasal, and 10.8% with placebo. This translated to a 68% relative reduction with the IM vaccine and a 36% reduction with the intranasal version, as compared to placebo. Comparing the 2 versions of vaccine, the IM inactivated vaccine resulted in 50% less influenza.

**Conclusions:** Although the IM inactivated and intranasal live attenuated vaccines both reduced rates of influenza, the inactivated formulation was significantly more effective.

**Reviewer's Comments:** With so much attention on influenza this year, younger patients are looking for advice on vaccination. The intranasal version of the seasonal flu vaccine is approved for healthy adults aged

Additional Keywords: None

Print Tag: Refer to original journal article
New Drug Shows Promise for Short-Term Use in ITP

Effect of Eltrombopag on Platelet Counts and Bleeding During Treatment of Chronic Idiopathic Thrombocytopenic Purpura: A Randomised, Double-Blind, Placebo-Controlled Trial.

Bussel JB, Provan D, et al.:
Lancet 2009; 373 (February 21): 641-648

Eltrombopag causes increased platelet counts and decreased bleeding in idiopathic thrombocytopenic purpura, but it has been studied only in short-term studies.

Background: Idiopathic thrombocytopenic purpura (ITP) can be mild or severe, but patients with severe ITP sometimes have limited treatment options.

Objective: To test a new thrombopoietin-receptor agonist, eltrombopag, for treatment of ITP.

Design: Randomized, placebo-controlled double-blind trial.

Participants: 114 patients who were aged >18 years, had had ITP for at least 6 months, had been treated for ITP on at least 1 previous occasion, and had a platelet count at study entry of ≤30,000.

Interventions: Eltrombopag 50 mg orally once daily versus placebo.

Results: 59% of patients in the treatment group had a platelet count of >50,000 on day 43 compared with 16% of the placebo group. There were no differences in response rate in those before and after splenectomy, and only a tiny, non-significant difference in those receiving ongoing ITP therapy. Those with initial platelet counts

Reviewer's Comments: Eltrombopag is an exciting new treatment for a condition that causes a few patients many problems. The drug has a number of important limitations, the most significant of which is the relatively short duration of the studies published so far. Long-term efficacy and adverse effects have yet to be established. It also has a significant issue with short-term use, in that it takes a week to show an increase in platelet count. These factors limit the current niche for eltrombopag to patients who need a short-term, but not immediate, boost in platelet count (eg, those undergoing elective procedures). It has recently been approved by the FDA for treatment of chronic ITP in patients who are at risk of bleeding and have responded poorly to conventional therapies. Its role in long-term maintenance therapy will depend both on the availability of data demonstrating safety and efficacy and on the pricing of the drug.

Additional Keywords: None

Print Tag: Refer to original journal article
Thiopurines Increase Risk of Lymphoma in IBD Patients

Lymphoproliferative Disorders in Patients Receiving Thiopurines for Inflammatory Bowel Disease: A Prospective Observational Cohort Study.
Beaugerie L, Brousse N, et al:
Lancet 2009; 374 (November 7): 1617-1625

Use of thiopurines (azathioprine, 6-MP) is associated with an increased risk of lymphoproliferative disorders in patients with inflammatory bowel disease.

Background: Thiopurines (azathioprine, 6-MP) are associated with lymphoproliferative disorders in patients with organ transplants. The drugs are also used in inflammatory bowel disease (IBD), but association with lymphoproliferative disease is unclear.

Design: Prospective, observational cohort study.

Participants: 19,486 patients with IBD, 5,867 of whom had ongoing thiopurine use.

Results: There were 23 cases of new lymphoproliferative disorders during the study, 1 case of Hodgkin’s lymphoma, and 22 cases of non-Hodgkin’s lymphoproliferative disorders. Of 23 patients with new lymphoproliferative disorders, 15 were on thiopurines at the time they developed symptoms, and 2 more had previously been on thiopurines. The unadjusted hazard ratio for lymphoproliferative disorder associated with thiopurine use was 3.25, but when adjusted for other risk factors such as older age, male sex, and longer duration of IBD, the adjusted risk attributable to thiopurines was 5.26. Of 15 patients on thiopurines at study entry, 12 had histology and clinical presentation consistent with post-transplant lymphoproliferative disorder.

Reviewer’s Comments: It is worth pointing out that the risk associated with poorly controlled IBD is significant, and if thiopurines were the only drugs available, benefits associated with using them would almost certainly outweigh any risks. However, they are not the only drugs available. The results of this study are significant for me, because I have started to look again at patients in my practice with IBD. I have a very low threshold for sending long-term azathioprine patients back to the gastroenterologist to determine if there might be an alternative. In the study cohort, there were relatively low rates of use of tumor necrosis factor inhibitors, and almost all patients on them were also on thiopurines. It was essentially impossible to assess the risk associated with these newer drugs in this cohort study. It is definitely worth keeping in mind that the absolute risk of lymphoproliferative disorder remains low, and this certainly should not be approached as an absolute contraindication to use of these very helpful drugs. However, a second look, particularly in patients on long-term therapy, may be worthwhile.

Additional Keywords: None

Print Tag: Refer to original journal article
Pending studies and the responsible follow-up provider are unlikely to be included in discharge summaries.

**Background:** Hospitalist medicine programs are on the rise, and fewer primary physicians are performing inpatient care. Accurate communication from inpatient providers to primary physicians is important to prevent medical errors. Studies that are pending at the time of discharge are common. At their best, discharge summaries list pending studies and the person responsible for follow-up, but the degree to which this occurs is not clear.

**Objective:** To understand how often discharge summaries accurately and completely include pending studies and best follow-up physician.

**Design/Methods:** Retrospective chart review of a random sample of discharge summaries from 2 large academic medical centers in Indiana, each with inpatient hospitalist services. Researchers used the electronic medical record (EMR) at these facilities to determine which studies were pending at the time of discharge; they also reviewed discharge summaries to determine if pending tests were documented and if a primary physician was mentioned. The authors coded how "actionable" each pending study was, as a way of determining the potential for that study result to change patient management.

**Results:** 696 patient admits/discharges were identified; 28 cases were excluded for patient death, transfer to hospice, or transfer to another hospital; 668 patient-cases were included in the final analysis. There were 2927 pending results at the time of discharge; of these, 296 (10%) were deemed "actionable," mostly microbiology, hematology, and chemistry studies. Only 16% of all pending studies and 28% of pending actionable studies were listed in discharge summaries as pending. Of all discharge summaries, only 25% mentioned pending tests. A primary care provider was listed in 50% of reviewed discharge summaries.

**Conclusions:** Discharge summaries appear to inadequately document pending studies and specific provider for follow-up; there is significant room for improvement.

**Reviewer's Comments:** The degree to which complete and effective handoffs occur at hospital discharge probably varies widely from hospital to hospital, and this study can only be generalized to similar academic medical centers with hospitalist physicians...but this study confirms what most of us already know: discharge summaries are often incomplete. This is a reminder to those who provide inpatient care to clearly document and communicate pending studies at the time of discharge, and to identify a point person for follow-up. It is a further reminder for those who provide outpatient care that discharge summaries received frequently miss important outstanding information. Automated lists of pending studies produced by EMR systems, if well designed, could help the inpatient physician be more efficient and effective in communications at patient discharge.

Additional Keywords: None

Print Tag: Refer to original journal article
Influenza is a negative-sense stranded RNA virus. Of the various strains, influenza A is the main concern because it makes up the bulk of human infections. Its genome is simple, consisting of only 8 genes.

(Card 1 of 2) Influenza is an ancient disease, and its name comes from the Italian word for “influence.” Centuries ago, it was believed that this constellation of symptoms (fever, myalgia, coryza, prostration, diarrhea, cough, and sometimes pneumonia or death) was caused by the influence of supernatural powers on humankind. Today, the source of influenza is well known. Influenza is a negative-sense stranded RNA virus. In fact, influenza comes in 2 main families, influenza A and influenza B, neither of which should be confused with the similarly named parainfluenza virus or the totally unrelated bacterium *Haemophilus influenzae*. Because it was originally isolated from the respiratory tracts of flu patients, *H influenzae* was thought, for a time, to be the cause of the flu, which we now know to be incorrect. Today, when we talk about the flu virus, we are referring to the influenza virus, especially influenza A. Influenza B is also a problem for humans and has the potential to make patients very sick. For this reason, the trivalent seasonal influenza vaccine always contains 1 influenza B antigen. However, influenza A is the main concern because it consistently makes up the great bulk of human infections. **Influenza A**: Influenza A’s genome is simple, consisting of just 8 genes. Two of the most important genes are for hemagglutinin (knob-like protein on virus’s surface that allows it to bind to respiratory epithelial cells) and neuraminidase (protein that allows new virions to bud from infected human cells, thus perpetuating the infection). Without both hemagglutinin and neuraminidase, influenza A would be rendered essentially harmless to human populations. The nomenclature of influenza A (H1N1, H3N2, etc) is based on the different combinations of antigens found on a given strain.

**Reviewer’s Comments:**

Additional Keywords: None

Print Tag: Refer to original journal article
Influenza's error-prone RNA genome means that minor changes in neuraminidase molecules are common, which can render our most valuable antiinfluenza drugs, the neuraminidase inhibitors, ineffective.

(Card 2 of 2) Influenza's error-prone RNA genome is both a boon and a burden. On the beneficial side, these viruses cannot permanently integrate their genes into human cells. In contrast, the DNA-based varicella-zoster virus or herpes simplex virus can become latent and cause clinical illness years later. However, with the influenza virus, once we are over a case of influenza, we are over it for good. In fact, we should be armed with B cell clones producing specific antiinfluenza antibodies that protect us significantly from subsequent infection with the same or even closely related strains. But there are downsides to fighting these negative-sense stranded RNA viruses. The high error rate inherent in passing RNA genomes from 1 generation to the next means that minor changes are common in the hemagglutinin (knob-like protein on virus’s surface; allows it to bind to respiratory epithelial cells) and neuraminidase molecules (allows new virions to bud from infected human cells). These changes can result either in small changes to the genome (antigenic drift) or in bigger changes involving whole chunks of RNA from other species (antigenic shift). In the spring of 2009, the so-called swine flu detected in Mexico resulted from an antigenic shift. This flu strain was derived from a strain that usually infects pigs instead of humans, and it was comprised of a unique never-before-seen mix of genes from North American bird and swine viruses, a Eurasian pig flu strain, and a human flu strain. This meant that a significant proportion of the world’s population, especially people aged 

**Neuraminidase Inhibitors:** The neuraminidase protein is the target of our most valuable antiinfluenza medications, the neuraminidase inhibitors, including oseltamivir and zanamivir. Mutations in the neuraminidase gene can render these medications ineffective. Oseltamivir resistance, in particular, has been demonstrated to evolve rapidly among patients on antiviral therapy. This RNA virus has considerable genetic infidelity, which poses a major challenge for clinicians worldwide.

**Reviewer's Comments:**

Additional Keywords: None

Print Tag: Refer to original journal article
The 2009 novel H1N1 flu strain was alarming because early reports of transmission in Mexico were well beyond the expected flu season peak and because a high number of children and young adults became severely ill.

Everyone who practices medicine in the northern hemisphere knows the hallmark of influenza transmission: its transmission occurs in a seasonal fashion. Each fall, we gear up for flu season, which typically peaks at slightly different times in different regions, but most often in February or March. It is not entirely clear why this has happened so predictably for so long. Common explanations include crowding of people during cold months and vulnerability of the respiratory epithelium due to dry air or coinfections with other respiratory pathogens. However, our colleagues who practice in equatorial and tropical regions of the world have had a different experience. In these regions, year-round transmission of influenza is the rule. In the United States, we finally had a taste of tropical flu transmission when, in April 2009, the world was stunned to read credible reports of influenza transmission in Mexico well beyond the expected peak of flu season. Two predominant strains of human influenza A had already circulated that season: human H3N2 and human H1N1. This new flu in Mexico underwent a variety of name changes during subsequent months, both in the lay press and in scientific journals. Today, its official name is the “novel swine-origin epidemic 2009 H1N1 influenza A strain.” The novel H1N1 influenza strain was alarming, not only because of its unusual timing, but also because of an unusually high number of children and young adults who seemed to become severely ill, sometimes fatally ill. Epidemiologists were worried early in the epidemic that we were making a classic blunder by reporting case-fatality rates based only on fatal cases. Without a reliable reporting system that looked at both mild and severe cases, we worried that the infection might appear to be more dangerous than it was in actuality. Indeed, this does seem to be the case. Because the epidemic has reached U.S. soil, we can use our excellent domestic public health surveillance system in conjunction with foreign surveillance services to better understand the communicability and the spectrum of clinical illness caused by H1N1. In late October 2009, H1N1 illness was already widespread in 46 states. Only Connecticut, Hawaii, New Jersey, and South Carolina are reporting sporadic rather than widespread infection.

Reviewer's Comments:

Additional Keywords: None

Print Tag: Refer to original journal article
The 2009 novel H1N1 influenza strain was alarming, not only because of its unusual timing (transmission began in off-peak season), but also because of an unusually high number of children and young adults who seemed to become severely ill. **2009 H1N1 Replaces Seasonal Strains:** As of late October 2009, the novel H1N1 influenza strain essentially has replaced seasonal flu infections. Most influenza isolates typed in the United States in the late summer and early fall of 2009 were H1N1. At that time, it remained unclear as to how long this would be true and whether expected seasonal strains (human H3N2 or human H1N1 from 2008) would rise to predominance in the coming February or March of 2010. My advice as of late October 2009 was that, if a patient had a clinical diagnosis of flu, he or she almost certainly had H1N1 flu. **2009 H1N1 Clinical Illness:** The clinical illness caused by the novel H1N1 influenza virus has been distributed across a broad spectrum similar to the regular seasonal flu. Fever and fatigue are the most common clinical findings, followed by various frequencies of myalgias, coryza, diarrhea, abdominal pain, and cough. Most patients infected with flu make a full, uneventful recovery, albeit with plenty of misery and missed work or missed school obligations. **2009 H1N1 & Poor Outcomes:** Although most patients infected with the H1N1 influenza virus will make a full recovery, some patients are at higher risk for poor outcomes. Some of these cases have not been previously considered to be in high-risk populations. A pair of papers from Mexico published in 2009 in *The New England Journal of Medicine* details the early experience with the epidemic in that country. One paper describes outcomes among >2000 patients with severe pneumonia reported to the Mexican Ministry of Health. The results of this study demonstrated that death rates were higher than in historical controls for patients aged 5 to 59 years. A second paper examined the experience of a single medical ICU in Mexico City. Eighteen cases of confirmed H1N1 pneumonia were described. Of those 18 patients, 13 were between the ages of 5 and 50 years. Most of the illnesses were severe; 10 patients required mechanical ventilation, and 7 of these died. **Reference 1:** Chowell, Bertozzi, et al. Severe respiratory disease concurrent with the circulation of H1N1 influenza. *N Engl J Med* 2009; 361 (August 13): 674-679. **Reference 2:** Perez-Padilla, de la Rosa-Zamboni, et al. Pneumonia and respiratory failure from swine-origin influenza A (H1N1) in Mexico. *N Engl J Med* 2009; 361 (August 13): 680-689.

**Reviewer's Comments:**

Additional Keywords: None

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Several possible risk factors associated with death due to the novel H1N1 influenza virus have been identified. These include pregnancy, obesity, synchronous presentation with *Staphylococcus aureus* pneumonia, and childhood.

As of late October 2009, young adults in the United States have borne a disproportionate and an unusually high burden of illness with the novel H1N1 influenza virus. The Centers for Disease Control and Prevention (CDC) estimates that there have been “many millions” of acute influenza cases. However, because we rarely test for and report cases anymore, this is indeed an estimate. The CDC has actually confirmed 22,080 cases of H1N1 flu among patients aged 5 to 24 years (case rate: 23 infections for every 100,000 people in that age range) and about 500 cases among patients aged >65 years (case rate: 1.3 per 100,000 population in that age range). This is a striking reversal of the usual epidemiology of flu. We strongly suspect that there have been >1000 deaths in the U.S. due to H1N1 as of late October 2009. Strictly speaking, the CDC has reported only 303 deaths, of which 82% have been among people aged

**Pregnancy:** Pregnancy is a risk factor associated with death due to influenza. At our Seattle medical center, a previously healthy woman in her third trimester of pregnancy was admitted with pneumonia, which rapidly progressed to acute respiratory distress syndrome, requiring prone ventilation with high positive end-expiratory pressures. The patient died shortly after an emergency C-section. The CDC’s *Morbidity and Mortality Weekly Report* in May 2009 detailed the cases of 3 pregnant women with H1N1, 1 of whom died (*MMWR* 2009: 58 [May 15]; 497-500). Similar cases have been reported in San Francisco.

**Obesity:** A possible link between body weight and severe illness was also suggested by a subsequent *MMWR* issue describing 10 critically ill patients in Michigan, 9 of whom were obese (*MMWR* 2009: 58 [July 17]; 749-752). At the time of the report, 2 remained critically ill and 3 had died. Autopsies revealed bilateral severe hemorrhagic viral pneumonitis with interstitial inflammation and diffuse alveolar damage, as well as concurrent bilateral pulmonary emboli. **Concurrent Pneumonia:** The classical teaching has been that patients with influenza pneumonia may develop *Staphylococcus aureus* pneumonia as a sequel, usually when clinical improvement for flu is well under way. However, a disturbing trend observed with the novel H1N1 outbreak has been the synchronous presentation of influenza and *S aureus* pneumonia. These cases may be severe necrotizing coinfections requiring mechanical ventilation, and several cases have been fatal. **Childhood:** Children are heavily affected by this novel H1N1 virus, even more so than during typical epidemics. In the U.S., the CDC is investigating >80 suspected flu deaths among children. The death rate is approximately double the typical annual child death rate during most entire flu seasons.

**Reviewer's Comments:**

Additional Keywords: None

Print Tag: Refer to original journal article
The Occupational Health and Safety Administration states that N95 masks should be worn by health care workers when within 6 feet of flu patients and should be discarded after each use.

With the outbreak of the novel H1N1 influenza virus, a very important prevention strategy is to practice diligent respiratory hygiene. Filter sneezes in disposable handkerchiefs or the crook of the elbow, then immediately clean hands with soap and water or an alcohol-based hand sanitizer. H1N1 flu is spread primarily via droplet nuclei. The central question is how health care workers should protect themselves against acquiring flu while on duty. **Droplet Controls:** The Infectious Disease Society of America, the Society of Hospital Epidemiologists of America, and the Association for Practitioners in Infection Control all agree: when caring for patients with suspected or proven flu (H1N1 or seasonal), protect yourself with diligent hand hygiene and wear gloves, a gown, eye protection, and a surgical mask. **N95 Masks:** One concern is that, in theory, influenza may also be transmitted by aerosolization, not just by droplet nuclei. Therefore, is an N95 mask superior to a regular surgical mask? N95 masks have been tested by the National Institute for Occupational Safety and Health, filter at least 95% of all particulate matter ≥0.3 µm in diameter, and are the same masks worn when caring for patients with active pulmonary tuberculosis. One study randomly assigned health care workers to either a surgical mask or an N95 mask. (*JAMA* 2009; 302 [November 4]: 1865-1871). Surgical masks were found to be noninferior to N95 masks in terms of protecting health care workers from influenza. However, investigators from Australia and China have described a yet-to-be published study in which health care workers were randomly assigned to wear either surgical masks, a fit-tested N95, or a plain N95 when caring for flu patients. Use of N95 masks was associated with a 75% decrease in the development of symptomatic flu. Based in large part on this study, the Centers for Disease Control and Prevention and the Institute of Medicine recommend use of N95 masks for health care workers when caring for flu patients. The Occupational Health and Safety Administration (OSHA) states that N95 masks should be worn when within 6 feet of flu patients. By OSHA rules, these masks should be discarded after each use. However, there are not enough N95 masks in the world to satisfy this requirement. If your supply of N95 masks starts to run low, one approach would be to use N95 masks for all influenza encounters but to wear surgical masks with eye guards on top of the N95 masks, and to swap out those surgical masks between encounters.

**Reviewer's Comments:**

Additional Keywords: None

Print Tag: Refer to original journal article
Among patients admitted to hospitals in China with seasonal flu, 30% continued to shed virus in their respiratory secretions beyond 7 days after fever resolution, even among those patients who had received antiviral medications.

During the 2009 novel H1N1 influenza outbreak, one of the major preventive strategies being taught to patients and health care workers alike is, “Stay home when you’re sick.” **Staying Home:** Physicians have a duty to care for their patients, and they often misinterpret this duty as an obligation to show up in the office or on the wards, regardless of how awful they feel. Yet, it is precisely this duty that mandates they protect their patients by staying away when sick. At the University of Washington Medicine, we have a very detailed coverage plan in case of health care worker illness, both for residents and faculty. A local residency program recently started its academic year with an orientation retreat for incoming interns. One participant had symptomatic H1N1 flu. Within about 1 week after the retreat, 19 of 33 interns were sick and had to be furloughed. The residency program already had a terrific contingency plan in place, so patient care was not significantly impacted. Please consider how a respiratory illness would affect you in your practice model. In my experience, patients are usually understanding and even grateful to know that their physician has the guts to reschedule due to a potentially transmissible illness. **Returning to Work:** When is it safe for health care workers to return to work after the onset of flu? We generally say that the general public (including school children) should reenter society only when they can control their nasal secretions and have been afebrile without use of antipyretics for at least 24 hours. However, the Centers for Disease Control and Prevention recommends that health care workers return to work at 7 days of afebrile status, simply because our patients tend to be so vulnerable to poor outcomes if we transmit our flu to them. For many hospitals and private practices, a week’s leave beyond fever resolution may seem impossible. If so, the second best option might be to consider allowing health care workers to return once afebrile for 24 hours, but requiring them to wear a surgical mask for the next week and allowing them to work only as long as they have enough stamina to do the work and the ability to control their nasal secretions. This sounds harsh, but consider a paper published by Lee and colleagues (**J Infect Dis** 2009; 200 [August 15]: 492-500). Among patients admitted to hospitals in China with seasonal flu, 30% continued to shed virus in their respiratory secretions beyond 7 days of fever resolution, even among those patients who had received antiviral medications.

**Reviewer’s Comments:**

Additional Keywords: None

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The intramuscular seasonal flu vaccine can be given to children aged 6 months to 19 years, pregnant women, adults aged ≥50 years, and people who live in nursing homes and long-term care facilities.

(Card 1 of 2) Influenza vaccination is a key portion of the influenza prevention plan every year. Guidelines for seasonal flu are slightly different than those for novel H1N1 influenza. Both seasonal flu and H1N1 vaccines have live-attenuated intranasal and inactivated intramuscular versions, all of which are made by different companies with different amounts of thimerosal. **Seasonal Flu Vaccination:** This year’s seasonal flu vaccine mix is very similar to last year’s. The influenza A portions are the same; only the influenza B antigen is different. Nonetheless, because the durability of influenza A following vaccination may wane over time, indications for the 2009 seasonal flu vaccine remain the same as for 2008, regardless of whether patients were vaccinated in 2008. The Advisory Committee on Immunization Practices (ACIP) recommends vaccinating anyone who wants a vaccination and who does not have a contraindication. They also ask that patients who are at increased risk for poor outcomes with influenza infection be targeted for vaccination. **Intramuscular Vaccination:** The intramuscular seasonal flu vaccine should be given to the following people: children aged 6 months to 19 years; pregnant women; adults aged ≥50 years; people of any age with certain chronic medical conditions including asthma, neuromuscular diseases, and immunosuppression (HIV and cancer); people who live in nursing homes and long-term care facilities; people who live with or care for those at high risk of complications from flu (health care workers, household contacts), and household contacts of children aged

**Contraindications:** Contraindications for the seasonal flu shot include severe allergy to chicken eggs; a Guillain-Barré outbreak within 6 weeks of a previous flu shot or some other severe vaccination reaction; or current illness with a fever. In some states, there may also be additional legal restrictions on whether pregnant patients can receive a certain vaccine containing a certain amount of thimerosal.

**Reviewer’s Comments:**

Additional Keywords: None

Print Tag: Refer to original journal article
FluMist®, a live-attenuated intranasal vaccine for seasonal influenza, is safe because the vaccine has been cold-adapted, meaning that it reproduces only in the nasal epithelial cells and not in the lower respiratory tract.

Influenza vaccination is a key portion of the influenza prevention plan every year. Guidelines for vaccinating for the seasonal flu differ between the intramuscular vaccine and the live-attenuated intranasal vaccine (FluMist®). **Intranasal Vaccine:** FluMist contains the same antigens as the intramuscular vaccine. Its safety is due to the fact that the vaccine has been cold-adapted, meaning that it reproduces only in the nasal epithelial cells and not in the lower respiratory tract. Nonetheless, because it contains live-virus particles and because it is a newer product with a shorter track record, it has a narrower target population. This vaccine is indicated for healthy people aged 2 to 49 years. Age restrictions for FluMist are narrower than for the intramuscular vaccine, and the list of host factors is also more restrictive. **Contraindications:** Patients should not get live-attenuated FluMist if they have reactive airways disease, are allergic to chicken eggs, are at increased risk of influenza complications (such as pregnancy), have HIV infection, or recently had a stem cell transplant. Health care workers who care for these patients generally can and should be vaccinated with either FluMist or the intramuscular vaccine. **FluMist for Health Care Workers:** Among health care workers caring for severely immunocompromised patients in certain exotic, protected environments (a stem cell transplant recipient or a baby in the neonatal ICU), those receiving FluMist should be furloughed for 7 days after vaccination. Although this has never been shown to hurt anyone, there is a theoretical concern that the virus might be passed from the nose of the health care worker into the respiratory tract of those very high-risk patients. **Miscellaneous:** FluMist is a superb vaccine for children because it is highly efficacious and very well tolerated. Some patients develop a bit of rhinorrhea or a sore throat after FluMist, but it is generally mild and brief.
The vaccine for the novel H1N1 influenza virus has 2 key points. Like the seasonal flu vaccine, the H1N1 vaccine also has both injectable and intranasal forms. In addition, the H1N1 vaccine has the same indications and contraindications as the seasonal flu vaccine. However, all of these recommendations presuppose an available stockpile of vaccine. In late October 2009, we were experiencing a very significant delay in the delivery of a robust quantity of both the live-attenuated and the intramuscular H1N1 vaccines. As of October 22, 2009, only about 11 million doses of these vaccines had been distributed nationwide. Many more doses were on order, and we were told that they would be delivered soon. Until that stockpile of vaccine grows significantly, clinicians and public health officers are faced with a challenging set of decisions regarding who should get vaccinated. **Priority List:** All guidelines that I have seen, including those from the Centers for Disease Control and Prevention, continued to keep 5 groups of patients at the top of the priority list. These groups included pregnant women, household and caregiver contacts of children aged Others: **Others:** All other patients should be vaccinated for novel H1N1 as well, including patients aged ≥65 years. However, because the relatively older crowd is somewhat protected against acquiring severe H1N1 flu, they should wait until the people at the top of the priority lists have consumed the early shipments of vaccine. **Health Care Workers:** Clearly, influenza vaccinations are safe, well tolerated, and significantly effective (although not entirely effective). Yet, according to position statements by the Infectious Disease Society of America, only about 2 of every 5 eligible health care workers undergo immunization annually. Help us improve this track record. Undergo immunization as soon as it is available in your community, and encourage your colleagues to do the same.

**Reviewer's Comments:**

Additional Keywords: None

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To prevent H1N1 influenza, offering postexposure prophylaxis, when appropriate, is a good preventive strategy. However, antiviral use does incur a potential price in terms of accelerating drug resistance.

During the 2009 outbreak of novel H1N1 influenza, offering postexposure prophylaxis, when appropriate, is one of several good preventive strategies. The risk of illness depends in some part on the type of exposure. An exposure is defined as coming within 6 feet of a symptomatic patient without wearing appropriate personal protective equipment. To help decide who should receive prophylaxis, ask the following questions. **Was the Exposure Real?** Has a medical doctor assessed the index patient and diagnosed flu based at least on clinical grounds? Generally, flu becomes a concern if the source patient has fever and is systemically ill. In addition, the exposed patient should have come within 6 feet of an infected individual. If these criteria are not met, then there is no need for prophylaxis. **When Was the Exposure? How Is the Exposed Patient Feeling?** If the exposure was >48 hours before presentation and if the exposed patient is feeling fine, then benefits of prophylaxis are very minimal. Instead, counsel this patient to contact you if he or she develops flu-like symptoms so that treatment can be started immediately. **Is the Exposed Patient at High Risk of Flu Complications?** These high-risk patients are the same individuals we target for influenza vaccination. For patients who are not at high risk for flu complications but are worried about it, prophylaxis is not required. However, for patients who are in a high-risk group, talk with them and select 1 of 2 courses. Either offer them prophylaxis on the spot or ask them to remain vigilant for signs and symptoms of flu and have them call you immediately if those symptoms should arise. **Judgment Calls:** When it comes to flu prophylaxis, use your judgment and rely on the relationship that you already have with the patient to craft an optimal plan. Some high-risk patients really want the recommended postexposure prophylaxis, which is fine. However, antiviral use does incur a potential price in terms of accelerating drug resistance. Nonetheless, I think that we should offer postexposure prophylaxis, especially when it is indicated for high-risk patients with a real exposure. **Drug Options:** If you offer prophylaxis, you can use either oseltamivir (75 mg by mouth once a day for 10 days in patients with normal renal function) or zanamivir (1 inhalation once a day for 10 days). The only contraindication to zanamivir is if the patient has reactive airway disease or if the patient cannot use the inhalation device. With oseltamivir, nausea may develop in some patients. This is temporary and generally mild. Most cases should respond to antinausea medication.

**Reviewer’s Comments:**

Additional Keywords: None

Print Tag: Refer to original journal article
Many providers use the rapid influenza test to help test for influenza infection. However, the test was not developed with H1N1 in mind, so very frequently the results are falsely negative.

In 2009, the diagnosis of influenza remains a clinical diagnosis for most cases. A diagnosis of influenza is considered when the patient has a febrile illness with some combination of prostration, coryza, myalgias, cough, and diarrhea. This is true for both seasonal flu and H1N1 flu. H1N1 infection has no special clinical features that rapidly distinguish it from other influenza infections: no rash, no enanthem, and no splenomegaly. As of late October 2009, H1N1 is the predominant form of flu being spread in the community.

**Lab Tests:** Routine lab testing results are not specific for H1N1. White blood cell count, lactate dehydrogenase, and serum sodium levels do not offer reliable hints for the flu. Like all clinically important viruses, influenza is too small to be seen by light microscopy. **Rapid Flu Test:** It is possible to test specifically for influenza infection. For many providers, the test of choice has been the rapid influenza test because it is relatively affordable and can be performed at point of care. A positive result on a rapid flu test can be helpful in distinguishing influenza from other respiratory viral infections. However, the rapid flu test has a poor negative-predictive value. This test was not developed with H1N1 in mind, so very frequently we will see falsely negative results on the rapid flu test. **Recommended Tests & Specimens:** Two major testing options are recommended for the 2009 flu season: the direct fluorescent antibody test with viral culture backup or a reverse transcriptase polymerase chain reaction assay. Both testing options are run directly on respiratory specimens (nasopharyngeal wash or swab). Confirm with your local virology lab which specimen they prefer. If a wash is acceptable, have the patient tilt his chin up slightly and hold his breath, and then squirt about 10 mL of preservative-free normal saline into a nostril. The patient then leans forward, and the saline runs out of the nose and into a specimen cup. For a swab, insert a synthetic tip swab (not a cotton swab) into the nostril until you meet gentle resistance. Then twirl it a few times before removing it, and stick it into a tube with viral transport media. Most patients tend to ask for the swab rather than the wash. However, the swab is actually tolerated less well and has a much higher rate of lab rejection due to low epithelial cell counts. While performing both these procedures, the health care worker should be wearing proper personal protective equipment.

**Reviewer's Comments:**

Additional Keywords: None

Print Tag: Refer to original journal article
The 2 major testing options recommended for the 2009 flu season are the direct fluorescent antibody test with viral culture backup and the reverse transcriptase polymerase chain reaction assay.

(Card 2 of 2) The testing options for influenza are few. However, a clinical diagnosis is almost always sufficient, so testing is only rarely required. Nonetheless, the 2 major testing options recommended for the 2009 flu season are (1) the direct fluorescent antibody (DFA) test with culture backup and (2) the reverse transcriptase polymerase chain reaction (RT-PCR) assay. **DFA Testing:** Most labs offer a DFA with culture rather than the RT-PCR because of operator experience, cost, and lab setup. The negative- and positive-predictive values of DFA with culture are far superior to those of the rapid flu test. However, if the DFA is negative, then subsequent culture results can take days to come back. **RT-PCR Testing:** In many cases, DFA and culture are negative, but the RT-PCR test is positive. RT-PCR is a great test based on its high sensitivity, rapid turnaround, and ability to type the flu if the lab offers type-specific primer. However, RT-PCR assays are not approved by the CLIA, so some labs are reluctant to offer them because of the required expertise with molecular testing. At the University of Washington, we rely on a homemade RT-PCR assay. We batch these tests every day at 10:00 AM, and the results come back no later than 6:00 PM the same day. **When to Submit Tests and Treat:** A DFA or RT-PCR test should be submitted when the patient is sick enough to be hospitalized or the patient will remain ambulatory and is at high risk for influenza complications and the clinical diagnosis is unclear. The results of both the DFA and RT-PCR tests will take time. However, for flu treatment to be beneficial, it must be initiated rapidly. Therefore, treat the patient on clinical grounds and start medications right away, even before the test comes back. Antiviral drugs can be discontinued if the test comes back negative. Or, if the suspicion for flu remains high and the patient is at high risk for poor outcomes, you may elect to continue treating for flu even with negative test results. Remember, no test has a perfect negative-predictive value. **Additional Testing:** For all patients who are seriously ill with suspected flu pneumonia, test aggressively for respiratory copathogens, especially for *Staphylococcus aureus*. In these critically ill patients, a deep pulmonary secretion specimen, such as bronchoalveolar lavage fluid or deep endobronchial suction material, should be examined by Gram stain and sent for culture. Poor outcomes happen even in flu pneumonia without bacterial coinfection. However, when copathogens are present, they must be targeted for treatment.

**Reviewer's Comments:**

- Additional Keywords: None
- Print Tag: Refer to original journal article
Prioritize Antiviral Use -- Look for Timing, Symptoms, Risks

Treating Influenza: Patient Selection and Timing.

Paul Pottinger, MD:

Paul Pottinger, MD - Special Presentation

Antiviral treatment can be started immediately for patients who are at high risk for flu complications and are symptomatic at presentation, even if they present beyond 48 hours after symptom onset.

Most patients will recover from the flu on their own. For patients with mild illness, conservative therapy with rest, sensible hydration, and antipyretics and analgesics (acetaminophen or ibuprofen) as needed are a good choice. Treatment doses of aspirin should be avoided among flu patients because of the concern for Reye syndrome, causing more harm than benefit. However, doses of cardioprotective baby aspirin can be continued in flu patients. **Patient Selection:** Antiviral medications should be started immediately for patients with suspected flu if they are at high risk for complications of flu and poor outcomes. These patients include those presenting with severe flu, especially lower respiratory tract disease by exam or chest x-ray; patients who are sick enough to be hospitalized; women who are pregnant or up to 2 weeks postpartum; immunosuppressed patients, including those with HIV or cancer or taking immunosuppressive medications; patients with chronic lung disease; children aged 65 years; and children or adolescents aged When Is It Too Late to Start Treatment? **When Is It Too Late to Start Treatment?** The greatest benefit to flu medications comes when the drug is started within 48 hours of symptom onset. For that reason, patients with mild illness and no risk for complications who may present beyond 48 hours of symptom onset will obtain a very small (if any) benefit from starting oseltamivir or zanamivir. Therefore, these patients generally should not be offered treatment. However, for patients who are at high risk for complications and who are still symptomatic when they present, antivirals can be started immediately, even if it is beyond 48 hours since symptom onset. Anyone sick enough with flu to be hospitalized should be put on treatment right away, regardless of how long they have been sick.

**Reviewer's Comments:**

Additional Keywords: None

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As of late October 2009, during the novel H1N1 influenza outbreak, we still have good news when it comes to treating flu. Oseltamivir and zanamivir are still highly effective against virtually all of the H1N1 circulating in the community. **Antiviral Resistance:** In the *Morbidity and Mortality Weekly Report* published by the Centers for Disease Control and Prevention, there are a few case reports on patients who developed oseltamivir resistance while taking the drug. In at least 2 of these cases, resistance happened among severely immunocompromised hematopoietic stem cell transplant recipients with symptomatic flu who were treated with oseltamivir for weeks because of persistent symptoms and persistent viral shedding proven by testing. In several other cases, otherwise healthy school-age children at summer camp were taking oseltamivir prophylaxis because some of their fellow campers were ill with the flu, and these kids developed flu despite use of antiviral prophylaxis because there was so much intense oseltamivir use among their close contacts. Presumably, the same phenomenon could happen with zanamivir, although the neuraminidase resistance mutations that are described so far seem to be specific for oseltamivir rather than zanamivir. Therefore, I believe we have reason to use both of these drugs prudently. **Old Antiviral Medications:** Other classes of antiinfluenza medications used in the past are not reliably effective against H1N1, including adamantine, rimantadine, and amantadine. At this time, we do not recommend using rimantadine or amantadine for treating influenza during the 2009 flu season. However, as the season progresses, that situation may change. **Effective Antiviral Medications:** H1N1 remains very susceptible to both oseltamivir and zanamivir, and both of these drugs are well tolerated. Standard dosing is appropriate for virtually all patients, although higher dosing can be considered for the few critically ill patients you may encounter. Lack of an IV form of these medicines has been a problem in these circumstances. Fortunately, we now have access to a new drug, Peramivir IV. This IV drug is a neuraminidase inhibitor and is on the short list of drugs that treat infection caused by the H1N1 virus.

**Reviewer's Comments:**

Additonal Keywords: None

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Help Patients Debunk Vaccine Rumors

Frequently Asked Questions: Influenza Vaccinations and the Risks of H1N1 and Guillain-Barré Syndrome.

Paul Pottinger, MD:

Paul Pottinger, MD - Special Presentation

An unpublished but much publicized Canadian study indicates that patients receiving an influenza vaccination last year are 2 times more likely to acquire H1N1 infection this year. These findings of have not been confirmed anywhere.

In your medical practice, you may encounter numerous questions regarding the influenza vaccine. Being prepared for these questions will only enhance your patients' confidence in the safety of the influenza vaccine. **Question 1:** If I get the seasonal flu shot, am I more likely to catch swine flu? **Answer 1:** There is an unpublished but much publicized study in Canada which reportedly indicates that patients who underwent influenza vaccination last year are about twice as likely to acquire H1N1 infection this year compared with those who did not get the vaccine. However, these unpublished results have not been peer reviewed, and nothing like this has been confirmed in the United States, Britain, Australia, or anywhere else. Therefore, until more information comes out, I would simply ignore this report and reassure patients that they should undergo vaccination for seasonal and H1N1 flu as appropriate. **Question 2:** Does the swine flu vaccine cause Guillain-Barré syndrome? **Answer 2:** In 1976, which was the last year that a so-called swine flu widely circulated in the United States, a small number of vaccine recipients were diagnosed subsequently with Guillain-Barré. Whether this was causally related to the vaccine has never been fully established, but reasonable estimates state that the increased risk of Guillain-Barré among vaccine recipients in 1976 was about 1 added case per 100,000 vaccine recipients. Subsequently, intensive surveillance efforts have shown that the excess risk of modern flu vaccines is no more than 1 case per 1,000,000 vaccine recipients. In fact, a paper published in the *American Journal of Epidemiology* in 2009 analyzed 775 episodes of Guillain-Barré in Great Britain. The relative incidence of Guillain-Barré within 90 days of influenza vaccination was 0.76. By comparison, the relative incidence of Guillain-Barré within 90 days of an influenza-like illness was 7.35. This finding suggests that the flu infection, not the flu shot, is associated with a relatively low risk of Guillain-Barré. In fact, taken at face value, an effective flu vaccine seems to offer about a 10-fold protection against Guillain-Barré. Mainly for legal reasons, the Food and Drug Administration's rules state that a prior episode of Guillain-Barré within 6 weeks of vaccination is currently considered to be a contraindication for any further flu vaccinations. **Reference:** Stowe, Andrews, et al. Investigation of the temporal association of Guillain-Barré syndrome with influenza vaccine and influenzalike illness using the United Kingdom General Practice Research Database. *Am J Epidemiol* 2009; 169 (February 1): 382-388.

**Reviewer's Comments:**

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According to a paper published in 2009, adults who receive the intramuscular vaccine are about 2 times better protected against acquiring flu as those who receive the intranasal vaccine. This finding was highly unexpected.

As you recommend influenza vaccination to your patients, you will often be questioned about the necessity of the vaccine and about which form (intranasal versus intramuscular) is the most effective. How you answer these questions may often determine if the patient will elect to receive adequate influenza protection for the year. **Question 1:** If I had the swine flu last year, do I really need the shot this year? **Answer 1:** Guidelines from the Centers for Disease Control and Prevention (CDC) state that, if your patient has had a laboratory-proven case of H1N1 flu as shown by a positive reverse transcriptase polymerase chain reaction assay, then there is no need to vaccinate that patient again. The illness itself is a huge antigenic challenge. It confers a durable immunity to future flu infections with H1N1. However, a prior clinical illness that has not been proven to be H1N1 should not affect our decision to vaccinate that patient. It is unclear how many patients who believe that they have had the flu are actually correct. There is no readily available, reliable, specific serological test to tell who has been exposed to what antigens. If such a test existed, it would probably cost more than the vaccine. The vaccine is safe and well tolerated, covers multiple strains in the case of seasonal flu, covers the most important strain in the case of H1N1, and is a boost to the immune system. The bottom line is, yes, we recommend vaccinating regardless of the patient’s perceived infection history. **Question 2:** Which is better, the nasal or the intramuscular form of the vaccination? **Answer 2:** Both forms of the influenza vaccine work well, and either one is much better than getting nothing at all. However, according to a paper published in 2009 (JAMA 2009; 301 [March 2]: 945-953), adults who received the intramuscular vaccine were 2 times better protected against acquiring flu as those who received the intranasal vaccine. This finding was highly unexpected. It is actually the opposite of our current thinking about influenza vaccine efficacy in children, where the nasal vaccine seems to be slightly more effective than the intramuscular form. But again, this is a relatively fine point. I think you should vaccinate with whatever the patient will accept and, frankly, with whatever you can get your hands on.

**Reviewer's Comments:**

Additional Keywords: None

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Most patients should do whatever they can to avoid catching the flu, including receiving influenza vaccinations regardless of the season. Remember, H1N1 outbreaks are being reported during traditional off-peak seasons.

Many rumors exist regarding the safety of influenza vaccinations. In addition, the popular media tend to give out conflicting information regarding influenza vaccines. This means that patients will come to you with questions about vaccinations. The better prepared you are for their questions, the more confident your patients will be with your answers. **Question 1:** Some patients in March, April, or even May of 2010 may ask you whether getting vaccinated is worth the effort at that time of the year. They are seeing you late in the season when flu outbreaks are typically done. So is there really any need to get vaccinated? **Answer 1:** They may be right, if they are lucky. Even seasonal flu can peak in March in some regions of the United States. However, the bigger point is that the H1N1 virus has demonstrated that the flu no longer watches the calendar as reliably as the seasonal flu has in the past. We simply do not know how or where it may surge back to life. Therefore, these patients should not worry so much about epidemiology. Tell your patients that they should focus on whether they want to get the flu. How would acquiring a case of influenza impact their life, their school, their income, and their childcare duties? When you state the problem this way, most patients do whatever they can to avoid catching the flu, which includes receiving influenza vaccinations, regardless of the time of year.

**Question 2:** Some patients have heard that oseltamivir can make an individual crazy or commit suicide. Is this true? **Answer 2:** This is a real question, and the answer is “no.” Reports from Japan in 2008 actually suggested that adolescents receiving oseltamivir for treatment of flu had an unexpectedly high incidence of psychosis, psychotic break, and self-harm, including suicide attempts. However, subsequent investigations into this topic did not substantiate a clear link with the drug as the cause of these clinical findings. The oseltamivir package insert discusses this topic and advises caution when dosing adolescents who have an underlying case of psychosis. However, my interpretation of this cautionary note is that it is more of a legal than a scientific disclaimer.

**Reviewer's Comments:**

Additional Keywords: None

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Pregnant women should get an influenza vaccination. The vaccine injection is both safe and highly effective in pregnancy. It does not cause the flu in the mother, and no link has been found between autism and the vaccine.

Women who are pregnant frequently have many concerns about receiving the influenza vaccine. They are concerned about whether they should actually receive the influenza vaccination in their condition. They may also fear catching a case of the flu from the shot. One of their big fears is that their baby will develop autism resulting from the mother being vaccinated. **Pregnancy & Vaccination:** Pregnant women should get an influenza vaccination. They are at an unusually high risk for poor outcomes with H1N1 flu. Although we do not understand exactly why this is true, we do know that it actually does happen. The good news is that the influenza vaccine injection is both safe and highly effective in pregnancy. It cannot cause the flu. **Vaccination & Autism:** Despite an exhaustive search by scientists around the world, no link has been established between thimerosal (a mercury-containing preservative in the vaccine) and autism. A series of biological and epidemiological studies have demonstrated that this fear of autism is unfounded. The American Academy of Pediatrics, the Centers for Disease Control and Prevention, and the Infectious Disease Society of America urge pregnant women to get vaccinated as soon as possible. On a personal note, a child in my own family has autism, and I always insist that this child and the whole family get vaccinated for flu each year. **Intranasal Vaccine:** The nasal FluMist® vaccine is probably safe in pregnant women, but it has not been studied in this population. Therefore, FluMist is relatively contraindicated in pregnant women.

**Reviewer's Comments:**
The 2009 H1N1 influenza vaccine has been made with the same technology used to manufacture the seasonal flu vaccine for many years. To date, the vaccine has no reported unusual or severe adverse events.

One of the rumors circulating about the H1N1 influenza vaccination is that the vaccine is not safe because it has not yet been tested thoroughly. Because of this, some patients will tell you that they are not interested in receiving the vaccine until it is proven safe. **Fact:** The 2009 H1N1 flu shot was brought to market in record time, which is a huge triumph for medical science. Undoubtedly, it will prevent many illnesses, and it has been made with the same technology used for seasonal flu vaccine for many years. During the vaccine’s manufacturing process, the H1N1 virus is grown in chicken eggs, and when the chicken eggs are purified, the virus is killed and moved into the vaccine vehicle. Clinical safety trials have been performed in the H1N1 vaccine, including at the University of Washington School of Medicine in Seattle. As of late October 2009, there are no reported unusual or severe adverse events associated with the vaccine. In the future, we possibly may find some reports of very rare adverse events, but by definition, we do not know if this will happen. In general, every year, we never know if that will happen. What we do know is that the risk of flu is very real, and that there is every reason to think that the H1N1 vaccine will be totally safe. **Safety Monitoring:** In August 2009, the Centers for Disease Control and Prevention (CDC) stated that vaccine safety monitoring is a shared responsibility among the federal government, state and local health departments, vaccine manufacturers, health care providers, and other partners. They established the Vaccine Adverse Event Reporting System as a frontline monitoring system for collecting and analyzing voluntary reports of adverse events following the 2009 H1N1 vaccination. The CDC will also monitor adverse events using the Vaccine Safety Datalink, which is a collaborative effort between the CDC and 8 large managed care organizations representing approximately 3% of the U.S. population. Many other safety-monitoring measures are at work.

**Reviewer's Comments:**

Additional Keywords: None

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