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Adverse Events Reported Following Live, Cold-Adapted, Intranasal Influenza Vaccine

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ANUAL INFLUENZA VACCINATION is the primary method for protection against influenza illness.¹ Until the 2002-2003 influenza season, the only licensed influenza vaccine in the United States was the inactivated, trivalent injectable vaccine, with recommendations emphasizing use among individuals for whom influenza is of particular concern.^{1,2} In June 2003, the US Food and Drug Administration (FDA) licensed a trivalent live, attenuated influenza vaccine (LAIV-T [FluMist, MedImmune Vaccines Inc, Gaithersburg, Md]) for intranasal use among healthy persons 5 to 49 years of age.³ Each dose contains live attenuated influenza virus reassortants of the 3 strains recommended by the US Public Health Service for the corresponding influenza season.^{2,3}

During prelicensure clinical trials, LAIV-T was administered to 20 228 persons aged 6 months to 93 years.³ Although the number of vaccinees studied during clinical trials was relatively large, postlicensure administration of the vaccine to much larger populations could reveal new safety

For editorial comment see p 2763.

Context In June 2003, the US Food and Drug Administration licensed a trivalent live, attenuated influenza vaccine (LAIV-T) for intranasal administration to healthy persons 5 to 49 years of age. Although prelicensure testing involved 20 228 vaccinees, clinical trials were not of sufficient size to detect rare adverse events reliably.

Objective To identify adverse events reported following LAIV-T administration after licensure.

Design, Setting, and Participants All adverse events reported to the US Vaccine Adverse Event Reporting System (VAERS) during the 2003-2004 and the 2004-2005 influenza seasons.

Main Outcome Measures Numbers and proportions of reported adverse events and reporting rates of adverse events per 100 000 vaccinees.

Results Approximately 2 500 000 persons received LAIV-T during the first 2 post-licensure seasons. As of August 16, 2005, VAERS received 460 adverse event reports for vaccinations received from August 2003 through July 2005. No fatalities were reported. There were 7 reports of possible anaphylaxis, 2 reports of Guillain-Barré syndrome, 1 report of Bell palsy, and 8 reports of asthma exacerbation among individuals with a prior asthma history. Events in individuals for whom the vaccine was not indicated accounted for 73 reports (16%).

Conclusions Reports to VAERS in the first 2 seasons of LAIV-T use did not identify any unexpected serious risks with this vaccine when used according to approved indications. Like many vaccines and other medical products, LAIV-T may rarely cause anaphylaxis. Secondary transmission of the vaccine virus merits further investigation. Reports of asthma exacerbations in vaccinees with prior asthma history highlight the risks of vaccine use inconsistent with approved labeling.

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issues.^{4,5} Currently, the vaccine manufacturer is conducting a large postlicensure study in a health maintenance organization to monitor medically attended and serious adverse events in a total of 60 000 LAIV-T recipients 5 to 49 years of age.⁶

The Vaccine Adverse Event Reporting System (VAERS), jointly operated by the FDA and the Centers for Disease Control and Prevention since 1990, accepts reports of adverse events from any source. Although a few reports are sent by vaccine recipients or their parents, most originate from health care clinicians. They may submit reports to VAERS directly or through manufacturers or state

health coordinators.^{4,5,7} Manufacturers are required by law to report adverse events. Reports are sent electronically, by mail, or by fax, and are received by a VAERS contractor who enters the information into a database. The contractor will contact the reporter if basic information is not included.

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All serious reports are reviewed by FDA physicians who evaluate whether further follow-up investigation is needed.

The objective of this study of adverse events reported to VAERS during the first 2 influenza seasons following LAIV-T licensure was to describe the characteristics of reported adverse events and to identify new or unexpected adverse events, including rare events.

METHODS

We reviewed all reported adverse events that followed LAIV-T administration during the 2003-2004 and the 2004-2005 influenza seasons (August 1, 2003, through July 31, 2005) and received by VAERS through August 16, 2005.

Reports are classified in VAERS as either serious or nonserious according to the information provided in the report. The *Code of Federal Regulations* defines serious adverse events as death, life-threatening illness, hospitalization or prolongation of hospitalization, permanent disability, or any event for which a medical intervention was required to prevent one of these outcomes.⁸ No causal relation to vaccination is implied by submission of an adverse event report.

Manufacturers are required to send all reports of adverse events to the FDA according to a specific timetable.⁸ Events that are serious adverse events and not included in the vaccine label are usually expedited in accordance with the *Code of Federal Regulations*. In addition, during the first 2 seasons following licensure, at the request of the FDA, the vaccine manufacturer also expedited reporting of other adverse events of interest. The events of primary interest for this review, based on severity, data from clinical trials, and adverse event experiences with other vaccines, included neurological events, possible anaphylaxis,⁹ possible secondary transmission of the vaccine virus to a contact, influenzalike illness, and possible asthma (BOX).

All reports and medical records were reviewed by 2 medical epidemiologists and were classified according to criteria

Box. Criteria for Review of Selected Conditions Following LAIV-T Administration

Neurological Event

Any report specifying a diagnosis/disorder of the nervous system

Possible Anaphylaxis⁹

Includes: (a) events with signs or symptoms developing within 4 hours after vaccination, involvement of 1 or more organ systems (cutaneous, respiratory, cardiovascular, and/or gastrointestinal) and treated with epinephrine, parenterally administered antihistamines, corticosteroids, intravenous fluids or bronchodilators or, if untreated, with involvement of more than 1 organ system; or (b) occurring more than 4 hours after vaccination, with involvement of more than 1 organ system and treated

Possible Secondary Transmission

Possible transmission of the vaccine virus to a contact either during administration of the vaccine or from a vaccine recipient

Influenzalike Illness

Events describing fever and cough, unless diagnosed otherwise

Asthma

Events with either a diagnosis of asthma/reactive airway disease or else describing wheezing, stridor, or bronchospasm, provided the report did not specify determination of an alternative diagnosis

Other Events

As specified in the report

described in the Box. Reports requiring clarification or additional information were investigated by telephone interviews with reporters or by requesting additional medical records.

Because VAERS is a government-sponsored surveillance system, institutional review board approval and informed consent were not required.

RESULTS

Approximately 2 500 000 persons received LAIV-T during the first 2 influenza seasons following licensure. Of these, approximately 500 000 were vaccinated during the 2003-2004 influenza season and approximately 2 000 000 were vaccinated during the 2004-2005 season (Kimber Poffenberger, MedImmune, written communication, April 18, 2005). VAERS received a total of 460 adverse event reports during the study period; a majority (283 reports) were received during the first season. Forty reports (9%)

were considered serious; no deaths were reported. Age (stated in 410 reports) ranged from 2 to 70 years (mean age, 26 years). Of 448 reports that specified sex, 256 (57%) occurred in females.

Allergic Events

Fifty-four reports (12%) were classified as allergic events (TABLE). According to criteria described in the Table, 7 reports were possible anaphylaxis events, including 4 in individuals who developed throat swelling (2 reported as serious) and 1 serious event in an individual who reported periorbital swelling. None of these events resulted in hospitalization. The age of individuals with possible anaphylaxis ranged from 10 to 49 years. The interval from vaccination to symptom onset was less than 3 hours for all cases, and 20 minutes or less for 5 of the cases. Although no one had a reported prior history of anaphylaxis or known allergy to any of the vaccine components, 5 cases had prior

history of hypersensitivity including contact dermatitis, hypersensitivity to other drugs, and seasonal allergy.

There were 47 reports of other allergic symptoms, mainly rash, urticaria, or edema, mostly in the face and neck.

Of these, 3 reports, including 1 of generalized urticaria, 1 of a generalized itchy rash, and 1 of rash on the back and chest, were reported as serious. The interval from vaccination to onset of symptoms was between 1 and 3 days for all 3 reports. None of these events resulted in hospitalization.

Table. Summary of All Intranasal Influenza Vaccine Reports by Main Condition, VAERS, 2003-2005

Main Conditions	No. (%)	
	All Reports (N = 460)	All Serious Reports (n = 40)
Respiratory (n = 217)		
Influenzalike illness	67 (14.6)	2 (5)
Vaccine failure	4 (0.9)	0
Rhinitis	40 (8.7)	0
Pharyngitis, tracheitis	42 (9.1)	1 (2.5)
Secondary transmission	22 (4.8)	1 (2.5)
Sinusitis	12 (2.6)	0
Asthma	12 (2.6)	5 (12.5)
Pneumonia	10 (2.2)	5 (12.5)
Other respiratory	8 (1.7)	1 (2.5)
Constitutional (n = 67)		
Weakness/tiredness	21 (4.6)	0
Fever	14 (3.0)	1 (2.5)
Headache	13 (2.8)	1 (2.5)
Dizziness	12 (2.6)	1 (2.5)
Arthritis	7 (1.5)	1 (2.5)
Allergic (n = 54)		
Possible anaphylaxis	7 (1.5)	3 (7.5)
Other allergic	47 (10.2)	3 (7.5)
Abdominal symptoms (n = 33)	33 (7.2)	1 (2.5)
Ear-nose-throat (n = 18)		
Epistaxis	13 (2.8)	0
Nose ulcer, redness	2 (0.4)	0
Ear infection	2 (0.4)	0
Oral herpes simplex	1 (0.2)	0
Ocular (n = 7)		
Edema	3 (0.7)	0
Retinal hemorrhage	1 (0.2)	1 (2.5)
Eye pain	3 (0.7)	0
Neurological (n = 10)		
Guillain-Barré syndrome*	3 (0.7)	3 (7.5)
Bell palsy	1 (0.2)	1 (2.5)
Febrile seizures	1 (0.2)	1 (2.5)
Encephalomyelitis	1 (0.2)	1 (2.5)
Encephalitis	1 (0.2)	1 (2.5)
Other†	3 (0.7)	0
Cardiovascular (n = 10)		
Pericarditis‡	3 (0.7)	2 (5)
Myocardial infarction	1 (0.2)	1 (2.5)
Chest pain/discomfort	6 (1.3)	0
Other (n = 44)§		
Vaccine administration error	18 (3.9)	0
Other reports	26 (5.7)	3 (7.5)

Abbreviation: VAERS, US Vaccine Adverse Event Reporting System.

*One of 3 reports of Guillain-Barré syndrome was excluded from analysis because of lack of supportive information.

†Includes 1 report each of dystonic tongue, paresthesia of tongue, and ataxia.

‡One report of viral pericarditis; the other report of pericarditis was of unknown origin (cultures not performed).

§Includes (serious) chickenpox, group A streptococcal infection, a psychiatric condition, rash/erythema, taste perversion, and irritability.

||If the reason for reporting is either a technical vaccine administration error or the vaccination of a person for whom the vaccine was not indicated, but without known adverse consequences.

Respiratory Events

There were 217 reports (47%) of respiratory events (Table). Sixty-seven events were influenzalike illnesses; none of these events resulted in hospitalization. Two events required emergency department treatment and were reported as serious, 1 in a 39-year-old man with dehydration 3 days after vaccination and another in a 5-year-old boy with a high fever who tested positive for influenza 1 month after vaccination. None of 40 rhinitis events resulted in hospitalization or were reported as serious. Of the 42 pharyngitis/tracheitis cases, 1 case, tracheitis in an 8-year-old boy with onset 22 days after vaccination, resulted in hospitalization. There were 10 reports of pneumonia with onset intervals between 1 and 45 days after vaccination. Two of them, 1 in a 30-year-old man with onset 7 days after vaccination and 1 in a 10-year-old boy with onset 2 days after vaccination, resulted in hospitalization. In 3 other pneumonia events (in a 9-year-old boy, a 13-year-old boy, and a 9-year-old girl) the patients were not hospitalized, but were reported as serious events. Among 12 sinusitis reports, none was reported as serious.

Possible Secondary Transmission

There were 22 reports of possible secondary transmission of the vaccine virus from vaccinees to nonvaccinees. None of the events resulted in hospitalization. Among 18 cases in which age was reported, ages ranged from 3 to 64 years. Among 17 reports for which this information was available, the interval from exposure to a vaccinated person to symptom onset ranged from a few hours to 15 days. Thirteen of the events (59%) were transmission to a

health care clinician who administered the vaccine. Of them, 6 events reportedly occurred among military medical personnel exposed to vaccinees who already had respiratory symptoms at the time of LAIV-T vaccination. One possible secondary transmission event reported as serious concerned a 3-year-old girl with influenzalike symptoms followed by lobar pneumonia 3 days after her mother received LAIV-T. Only 1 report of suspected secondary transmission included laboratory analysis to distinguish between vaccine and wild-type strains. Fifteen days after a pediatrician received LAIV-T, her 4-year-old child developed influenzalike symptoms. The Centers for Disease Control and Prevention influenza laboratory analysis revealed that the child's isolate was wild-type influenza A(H3N2) similar to A(H3N2) viruses that had been circulating and did not contain any gene of the vaccine strain. There was no report of possible secondary transmission to an immunosuppressed individual.

Possible Asthma

Of 12 asthma episodes reported, 9 were among children 6 to 15 years of age and 3 in adults. The interval from vaccination to symptom onset ranged from a few hours to more than a month. In 6 asthma events, the interval was 4 days or less. Eight of the 12 reports involved asthma exacerbations among persons with prior asthma history. Five were reported as serious.

Neurological Events

Ten neurological events (2%) were reported, and 7 were reported as serious (Table). Two of the reports were Guillain-Barré syndrome (GBS), both confirmed by a neurologist. The first was in a previously healthy 21-year-old woman who received LAIV-T in December 2004. The day following immunization she developed fever and myalgias (her mother, who was not vaccinated, had similar symptoms as well as pneumonia). About 10 days postvaccination, she developed paresthesia in her extremities, and 8 days later

facial weakness, progressive limb weakness, and loss of most reflexes. The lumbar puncture found high protein concentration (273 mg/100 mL) in the cerebrospinal fluid and no pleocytosis. She was hospitalized and recovered. Guillain-Barré syndrome was also reported in a previously healthy 50-year-old man with symptom onset 1 day after vaccination. His son and wife had had a gastrointestinal illness approximately 2 weeks earlier.

Bell palsy was reported in a 40-year-old woman with onset of symptoms 5 days after vaccination. No cause was identified. Although she reported a prior episode of Bell palsy approximately 20 years ago, this could not be confirmed. Acute disseminated encephalomyelitis (ADEM) was reported in a 14-year-old boy with a prior history of asthma. On the day of vaccination he had an upper respiratory tract infection. Two days postvaccination, he developed confusion, followed by hyperreflexia and meningismus. Magnetic resonance imaging was consistent with ADEM, and a nasal swab was negative for influenza viruses. He was treated as an inpatient with corticosteroids and improved within 24 hours. Laboratory-confirmed enterovirus encephalitis was reported in a 39-year-old pediatric nurse with onset 10 days after vaccination. Another report concerned a 4-year-old boy with no prior history of seizures who experienced febrile seizures approximately 26 hours after receiving LAIV-T. He recovered without sequelae. There were 3 nonserious reports of other neurological conditions, including dystonic tongue 3 days after vaccination in a 10-year-old boy with prior history of a similar episode, tongue paresthesia in a 41-year-old man 1 day after vaccination, and ataxia and vertigo in a 52-year-old individual with onset 11 days after vaccination.

Abdominal Symptoms

There were no reports of intussusception among 33 reports (7%) of abdominal symptoms, which included abdominal pain, vomiting, and diarrhea. There was only 1 serious report, of hospitalization, in a 46-year-old man diag-

nosed with "viral" gastroenteritis leading to ileus with onset 6 days after vaccination. No cultures were performed.

Constitutional Symptoms

Of 67 reports (15%) of constitutional symptoms, the most frequently reported events included weakness/tiredness (21), fever (14), headache (13), dizziness (12), and arthritis (7) (Table).

Ear, Nose, Throat, and Ocular Symptoms

Of a total of 18 reports (4%), 13 were epistaxis, 2 were nasal ulcer or redness, 2 were ear infections, and 1 was oral herpes simplex. None were serious. Seven reports (2%) described ocular symptoms, including 3 reports of eye edema, 3 reports of eye pain, and 1 (serious) report of retinal hemorrhage in a 9-year-old boy 1 day after vaccination. For the latter report, the ophthalmologist reported bleeding in the retina but no detachment. None of these events resulted in hospitalization.

Vaccination of Persons for Whom the Vaccine Was Not Indicated

There were 73 reports (16%) involving individuals for whom the vaccine was not indicated according to the product label. Of them, 21 were outside the recommended age, 47 had preexisting chronic conditions, and 5 were both outside the recommended age and had preexisting chronic conditions. The most frequent adverse events reported among persons for whom the vaccine was not indicated were influenzalike illness, rhinitis, and other respiratory symptoms (31 reports).

Of the 26 total reports among individuals outside the recommended age (including 5 who also had chronic conditions), 7 were younger than 5 years and 19 were 50 years or older.

Among 52 reports for individuals with preexisting chronic conditions (including 5 who were also outside the recommended age), 16 patients had a prior history of bronchospasm. Eight reports involved asthma exacerbations af-

ter vaccination. Three of these events were serious: 1 report involved a 14-year-old boy with onset 2 days after vaccination who had status asthmaticus and was hospitalized; another report involved a 6-year-old boy with onset 3 days after vaccination with symptoms lasting for 7 days; and the remaining report was of a 7-year-old boy with onset of wheezing within 4 days after vaccination.

Among 8 reports concerning individuals with a prior history of chronic cardiovascular disease, 1 serious case involved a 42-year-old man with a history of uncontrolled hyperlipidemia who was hospitalized with a myocardial infarction 2 days after vaccination. Among 10 reports from individuals with preexisting metabolic conditions (including 8 with thyroid disease), 1 (a 48-year-old woman who had pneumonia 7 days after vaccination) was serious. There were no hospitalizations. Among the remaining 14 individuals with chronic conditions (4 with chronic neurological conditions, 4 with chronic respiratory diseases, 2 with pernicious anemia, 2 with sarcoidosis, 1 with fibromyalgia, and 1 with lupus), none resulted in hospitalization. One report, in a 48-year-old woman who had a prior history of Bell palsy, was classified as serious.

Vaccine Administration Error

There were a total of 18 reports (4%) in which the only reason for reporting was an error in vaccine administration with no known adverse consequences. These included administration of 2 doses instead of 1 to children 9 years of age or older (10 reports), improper handling of vaccine (5 reports), and vaccination of a pregnant woman (2 reports).

COMMENT

A major strength of VAERS is that it is national in scope. VAERS may allow detection of rare events that would be unlikely to be detected even in large clinical trials. In the case of LAIV-T, these included anaphylaxis and neurological

events. In addition, epistaxis, although among the more frequent events, also was not investigated during clinical trials. However, because of the limitations inherent in passive surveillance—including underreporting, reporting of solely temporal associations, unconfirmed diagnoses, lack of denominator data and unbiased comparison groups, and possible reporting, surveillance, or source bias—data from VAERS require cautious interpretation.^{4,5,7} The rates of spontaneous adverse event reports can be higher within the months following initial marketing of a new product,¹⁰ and serious adverse events are more likely to be reported.

According to the package insert, LAIV-T is contraindicated for individuals with a history of anaphylactic reactions or hypersensitivity to any of its components, including eggs or egg products.³ In this review, none of the reports of possible anaphylaxis described a prior history of anaphylaxis or hypersensitivity to a vaccine component. The 5 reports of possible anaphylaxis with onset within 20 minutes after vaccination are consistent with causal association. This rate of 2 anaphylaxis reports per million vaccinees is within the range from 1 per 20 000 to 1 per million estimated by the Institute of Medicine for anaphylaxis after measles-mumps-rubella vaccination and is somewhat higher than the 0.65 cases per million doses reported for all childhood and adolescent vaccinations in 4 health maintenance organizations.^{9,11} Although this estimate of anaphylaxis incidence in VAERS could be affected by underreporting, serious events are more likely to be reported.^{4,5,12}

Shedding of vaccine virus following LAIV-T administration has been observed in clinical trials, particularly among children, and transmission of vaccine virus has been documented in a child care setting in a clinical trial in Finland.¹³ The per-protocol rate of transmission was 1.75% (1/57), with an upper boundary of the 95% confidence interval of 8.05%. Among the 22 reports of secondary transmission in VAERS, only 1 report provided information

about virus isolation and characterization, and in it the virus found was a wild-type influenza A(H3N2) virus. The other reports of suspected secondary transmission were not assessed with virus isolation and characterization. In the absence of viral characterization, reports of possible secondary transmission events may represent coincidental, naturally occurring respiratory infections. Because reporting delays and lack of laboratory resources hinder the role of VAERS in the investigation of secondary transmission, any further investigation of this potential risk would have to take place in settings other than VAERS.³⁻⁵ The fact that more than half of these reports were of transmission to a health care worker who administered the vaccine may reflect preferential reporting related to concerns of the medical community regarding this potential risk.^{2,3}

With regard to the 2 GBS reports, both diagnoses were confirmed by a neurologist. In 1 case, the short interval between vaccination and symptom onset, and the patient's recent exposure to family members with gastrointestinal illness, which provides an alternative nonvaccine etiology, make the association with the vaccine less likely.^{14,15} For the second case, the etiology of the GBS cannot be identified. Although the patient's respiratory infection of unknown origin presents an alternative nonvaccine etiology, the interval from vaccination to onset is compatible with prior research on GBS and inactivated influenza vaccine.^{14,15} As for the ADEM report, the short time interval does not appear to support vaccine causation.¹⁶

Because of the route of administration of this vaccine and timing of the adverse events, the VAERS reports of epistaxis, nose ulcer, and ocular symptoms are potentially compatible with vaccine causation. The 73 reports of vaccination to persons for whom it was not indicated, and the 18 reports of vaccine administration errors, underscore the complexity of marketing a vaccine that requires a new route of administration and is indicated for healthy people belonging to a specific age group.

Although data from a large community-based trial did not support the hypothesis that LAIV-T is associated with an increase in asthma events in children,¹⁷ the 8 reports of asthma exacerbations among persons with prior history in our study are consistent with findings from a small multicenter, prospective, randomized, double-blind, placebo-controlled safety study among moderate and severe asthmatics 9 to 17 years of age. In that study, 2 of 24 LAIV-T recipients (days 2 and 3 post-vaccination) and 0 of 24 placebo recipients had asthma exacerbations within 28 days.¹⁸ Additionally, a significant increase in asthma or reactive airways disease was observed for children 12 to 59 months of age following the first dose of LAIV-T in a randomized, double-blind, placebo-controlled trial.¹⁹

CONCLUSIONS

Reports to VAERS in the first 2 seasons of LAIV-T use did not identify any unexpected serious risk with this vac-

cine when used according to approved indications. Like many vaccines and other medical products, LAIV-T may rarely cause anaphylaxis. As with other vaccines, LAIV-T could carry the risk of anaphylaxis or other allergic events. Continued monitoring of neurological events, such as GBS, appears warranted. Determination of the risk of secondary transmission of the vaccine virus would require a focused clinical study.

The reports of asthma exacerbations in vaccinees with prior asthma history highlight the potential risks of not following the approved indications and support the need for continued close surveillance for asthma exacerbations following use of this vaccine. The finding of a high proportion of vaccine administration errors and the reports of use among persons for whom this vaccine was not indicated underscore the need for the clinician to follow the package insert indications regarding vaccine administration and patient eligibility.

Author Contributions: Dr Izurieta had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Izurieta, Haber, Wise, Mink, Ball.

Acquisition of data: Izurieta, Braun.

Analysis and interpretation of data: Izurieta, Haber, Wise, Iskander, Pratt, Mink, Chang, Braun, Ball.

Drafting of the manuscript: Izurieta, Haber, Wise.

Critical revision of the manuscript for important intellectual content: Izurieta, Haber, Wise, Iskander, Pratt, Mink, Chang, Braun, Ball.

Statistical analysis: Izurieta, Chang.

Administrative, technical, or material support: Izurieta, Wise, Iskander, Braun, Ball.

Study supervision: Izurieta, Haber, Wise, Iskander, Pratt, Mink, Braun, Ball.

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That approach leaves several critical issues unresolved. First, federal policy actively discourages high-quality research by making access to marijuana by researchers exceedingly difficult. Even when access to marijuana is finally granted, there is substantial variability in the purity and content of the product. Second, researchers need to test the assumption noted by Das that THC is the active ingredient responsible for the perceived beneficial effects. Although that assumption is reasonable, there remains the possibility that marijuana, not THC in isolation, achieves the desirable effects. Third, researchers should test the most efficient delivery system. There may be some added value in smoking that needs to be evaluated.

If research concludes that THC is the beneficial ingredient and that delivery by tablet is safest and most effective, then there is justification for approval of that method only. A synthetic THC oral medication (dronabinol) is already available for prescription with US Food and Drug Administration-approved indications for anorexia associated with weight loss in patients with AIDS and for nausea and vomiting associated with cancer chemotherapy in patients who have failed to respond adequately to conventional antiemetic treatments.

Regulation of the use of marijuana for medical purposes is feasible and socially desirable, but it will require a different way of thinking about the problem. It requires viewing marijuana as a potential medication subject to carefully controlled research, rather than as a drug of strict prohibition.

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CORRECTIONS

Author Contribution Omissions: In the Original Contribution entitled "High-Dose Atorvastatin vs Usual-Dose Simvastatin for Secondary Prevention After Myocardial Infarction: The IDEAL Study: A Randomized Controlled Trial" published in the November 16, 2005, issue of *JAMA* (2005;294:2437-2445), several contributions were omitted for the author Anders G. Olsson, MD, PhD. In addition to his contributions listed in the article, Dr Olsson contributed to the study concept and design, acquisition of data, drafting of the manuscript, and statistical analysis for the IDEAL trial.

Duplicated Text: In the Original Contribution entitled "Neurologic Adverse Events Associated With Smallpox Vaccination in the United States, 2002-2004" published in the December 7, 2005, issue of *JAMA* (2005;294:2744-2750), a section of text was duplicated. The first 4½ lines on the top of page 2747 should be deleted. Thus, the last sentence on the bottom of page 2746 and continuing onto 2747 should read: "Of the remaining 3 cases, one man had probable encephalitis defined by altered mental status, pleocytosis, and multifocal demyelinating lesions on brain MRI 10 days after primary vaccination."

Incorrect Wording and Data: In the Original Contribution entitled "Combined Tetanus, Diphtheria, and 5-Component Pertussis Vaccine for Use in Adolescents and Adults" published in the June 22/29, 2005, issue of *JAMA* (2005;293:3003-3011), incorrect wording appeared at the end of the Results section. On page 3009, lines 15-16 of the fourth paragraph, ". . . the complaint resolved within 1 day" should read "the patient was hospitalized for 1 day and the complaint subsequently resolved without sequelae." In addition, in Table 4, for the entry "Axillary node swelling," in column 2 (Tdap Adolescents) 676 should be 67.

Incorrect Data: In the Original Contribution entitled "Adverse Events Reported Following Live, Cold-Adapted, Intranasal Influenza Vaccine," published in the December 7, 2005, issue of *JAMA* (2005;294:2720-2725), there were incorrect data in the first full paragraph on page 2724. The corrected paragraph is reprinted below:

Among 11 reports concerning individuals with a prior history of chronic cardiovascular disease, 1 serious case involved a 42-year-old man with a history of uncontrolled hyperlipidemia who was hospitalized with a myocardial infarction 2 days after vaccination. He underwent cardiac catheterization. Among 10 reports from individuals with preexisting metabolic conditions (including 8 with thyroid disease), 1 (a 30-year-old man hospitalized with pneumonia 7 days after vaccination) was serious. There were no other hospitalizations. Among the remaining 15 individuals, 13 had chronic conditions (3 with chronic neurological conditions, 4 with chronic respiratory diseases, 2 with pernicious anemia, 2 with sarcoidosis, 1 with fibromyalgia, and 1 with lupus) and 2 were pregnant; none resulted in hospitalization. One report, in a 48-year-old woman who had a prior history of Bell palsy, was classified as serious.