

## CORRESPONDENCE

### The Smallpox Immunization Program Compared with Clinical Research

*To the Editor:*—There are many similarities between the smallpox immunization program and clinical research. Both are voluntary and require some sacrifice and inconvenience of the subject. Most importantly, both involve a consideration of the balance between risks and benefits.

The risk of the smallpox vaccine is well known. The risk associated with the vaccine is low, based on data from the vaccination of 14.2 million people in the United States in 1968. There were 3.7 serious complications and 0.06 deaths per million vaccinated.<sup>1</sup> The knowledge of these risks may be influencing the willingness of others to volunteer for the vaccine.

These compare with the limited knowledge of the risk associated with a new drug or therapy being evaluated in a clinical research trial. The risks of a new drug or therapy are usually low but potentially much higher than the risk of the smallpox vaccine because of limited experience with its use. For example, the risk from a drug for a phase 3 clinical trial is based on data from phase 1 and 2 studies that typically have only enrolled about 100 to 380 subjects. The risk of a recently approved Food and Drug Administration (FDA) drug is based on data from phase 1, 2, and 3 trials plus some postmarketing cases of adverse reactions, which means it might have only been evaluated in about 3,380 subjects.<sup>2</sup> The risk of any newly approved FDA drug used in a clinical research study would probably be considered low if there were no reported serious adverse event in 50,000 patients. However, because of the relative limited experience with new drugs, the incidence of serious adverse events may actually be 1 in 200,000 or 1 in 1,000,000—much higher than the risk of the smallpox vaccine. Even though the estimated risk of a new drug is low, because of limited experience, the risk may potentially be much higher and possibly even higher than the risk of the smallpox vaccine.

The risk of participating in the smallpox immunization program and a clinical research trial must be compared with the potential benefits. The potential benefits of a clinical research trial also can be compared with the potential benefits of the smallpox immunization program.

Individuals are not expected to benefit from receiving the smallpox vaccine, even when compared with the low risk of the vaccine. The AAEM /SAEM smallpox vaccine work groups estimated the individual benefit of receiving the smallpox vaccine to be negligible based on the low probability that any individual physician would see the first few cases of smallpox and that post exposure vaccination would provide protection.<sup>3</sup> This lack of individual benefit is similar to the benefits a subject can expect from participating in a randomized, clinical trial. First, in most clinical trials, it is unknown if the subject will receive any benefit, because it is unknown if the new drug or therapy is effective. There usually are data suggesting a benefit; however, the true benefit is unknown, and this forms the basis for the research study. Additionally, if there are side effects or toxicities from

the drug or therapy, the placebo-treated individual may actually be the one to benefit by not being exposed to the toxic and/or ineffective new drug. Second, if there is a benefit from the drug or therapy, only 50% of participants will receive it in a randomized, clinical trial. Although most subjects participate in research expecting to individually benefit, it is unknown if they will individually receive any benefit. The smallpox immunization program and clinical research can be compared with respect to potential individual benefits. Participation is not expected to result in direct benefit to the individual.

One of the benefits of participating in clinical research is the anticipated benefit not to the individual, but to society. This usually takes the form of knowledge gained from studying a drug or therapy, or knowledge gained from studying a disease process.

Similarly, by participating in the smallpox program, the anticipated benefits are not to the individual, but to society. The smallpox immunization program is a public health initiative, designed to create smallpox response teams at each acute-care facility to evaluate and manage suspected smallpox cases. Because historically most cases of smallpox transmission occurred in the hospital setting, these teams would decrease the spread of disease. The expected benefit to society is to decrease smallpox deaths and is based on mathematical modeling incorporating disease spread, vaccine complication rates, pre- and postexposure vaccination of health care workers, use of containment hospitals with vaccinated workers, and small versus large release of smallpox.<sup>4</sup> Based on this model with prior vaccination of health care workers versus postattack vaccination of health care workers, approximately 10,000 lives would be saved following a high-impact airport attack, 500 lives saved following a low-impact airport attack, and 80 lives saved following a building attack.<sup>4</sup> The smallpox immunization program and clinical research can be compared with respect to potential benefits to society. Participation is not expected to result in a benefit to the individual; however, participation may result in potential benefits to society.

There has been a slow start to the federal plan for smallpox immunization of health care workers. As of May 30, 2003, of an expected 200,000 eligible health care workers, only 37,337 have been vaccinated.<sup>5</sup>

The smallpox immunization program puts all those involved in clinical research (physician researchers, principal investigators, co-investigators, study nurses, institutional review board member, or anyone involved in recruitment and consent of clinical research subjects) in a position similar to their research subjects. Both the immunization program and clinical research are voluntary, require some sacrifice and inconveniences on the part of the subjects, expose the subject to a low level of risk, usually have no definite individual benefit, and potentially may benefit society. For those involved in clinical research, the

smallpox program provides an opportunity to evaluate the same types of decisions that research subjects are asked to make. A comparison of the risk and benefits of the smallpox immunization program to the risk and benefits of clinical research may put the vaccine in perspective and help clinical researchers make a decision about participation in the immunization program.—**Theodore C. Bania, MD, MS** (toxtod@aol.com), *Columbia University, St. Luke's–Roosevelt Hospital Center, New York, NY*; and **Gregory L. Almond, MD, MPH, MS**, *New York Medical College, Metropolitan Hospital Center, New York, NY*

doi:10.1197/S1069-6563(03)00596-7

## Society for Academic Emergency Medicine (SAEM) Neurologic Emergencies Interest Group Response to the SAEM Board Position on Optimizing Care of the Stroke Patient

*To the Editor:*—The issue of thrombolytic treatment of acute stroke patients has been polarizing in our specialty, with emergency medicine physicians lining up on both sides of the issue. The Society for Academic Emergency Medicine (SAEM) Board of Directors recently developed a position statement on “Optimizing Care of the Stroke Patient,” published in the May/June 2003 *SAEM Newsletter* and in the July 2003 issue of *Academic Emergency Medicine*.<sup>1,2</sup> This follows position statements on thrombolytic therapy for acute stroke by the American College of Emergency Physicians (ACEP), the American Academy of Emergency Physicians (AAEM), and the Canadian Association of Emergency Physicians (CAEP).<sup>3–5</sup> These opinions clearly are driven in large part by the concerns of some practicing emergency physicians who fear medicolegal liability for failing to treat patients with tissue plasminogen activator (t-PA) for acute stroke, as stated in the preamble to the AAEM position statement. The overriding issue seems to be that each group is trying to find reasons to say that t-PA treatment should not be considered standard of care for patients with acute stroke, although they differ in their reasons for this position.

The position of the SAEM Board of Directors is that “it is not yet clear whether the treatment risk is outweighed by the likely therapeutic benefit” for treatment of acute stroke with thrombolytic agents. This statement is at odds with available data. The original National Institute of Neurological Disorders and Stroke (NINDS) trial showed a statistically significant benefit for t-PA treatment over placebo, with an odds ratio of 1.7 for a neurologically normal outcome after t-PA treatment.<sup>6</sup> A recently completed independent statistical analysis of the original NINDS Stroke Study data was presented at the 2003 SAEM Annual Meeting in Boston.<sup>7</sup> The independent analysis stated that the odds ratio is 2.1 rather than 1.7, in favor of a good outcome. A pooled analysis of the NINDS, Alteplase Thrombolysis for Acute Noninterventional Therapy in Ischemic Stroke (ATLANTIS), and Euro-

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pean Cooperative Acute Stroke Study (ECASS) data further demonstrated a clear benefit to thrombolytic therapy, with the odds ratios for favorable outcome of 2.8 and 1.5 for patients treated within 0–90 and 91–180 minutes from onset, respectively.<sup>8</sup> These analyses considered that some patients are harmed by t-PA when computing the odds ratios, and yet benefit is clear, so the statement that there is uncertainty whether the treatment risk outweighs the benefit is not borne out by the data.

The position statement suggests that there is uncertainty whether these results can be expected when thrombolytic treatment is given outside of an institution without a streamlined system for delivering this care. With the exception of the original article by Katzan et al. from Cleveland, nearly all papers examining the delivery of t-PA outside of investigational studies have demonstrated intracerebral hemorrhage (ICH) rates that do not exceed the rates seen in the NINDS trial.<sup>9–14</sup> Even the Cleveland clinical setting, after initiation of a stroke quality improvement program, now experiences an ICH rate similar to that reported in the NINDS trial.<sup>9</sup> Moreover, data from the University of Michigan and others suggest that thrombolytic therapy administered by emergency physicians, with neurology consultation available, can deliver the same results seen in the trials performed by neurologists.<sup>15,16</sup> Clinical practice is derived from clinical research, and we can achieve the benefits of new advances by following the protocols developed through clinical research.

In the position statement, the Board of Directors also stated that advocating the stroke center approach is well intended, but that such designation should await outcomes data that demonstrate the overall systems benefit of such centers. These data exist as well. There are numerous articles documenting improved outcomes when institutions have designated services to acute stroke.<sup>17–21</sup> Furthermore, these improved outcomes apply to all stroke patients and are not restricted to those receiving or not receiving

interventional acute stroke care.<sup>22,23</sup> In fact, organized multidisciplinary stroke care is one of few interventions that have been proven to benefit stroke patients outside of the use of t-PA.<sup>22</sup>

The question for academic emergency physicians should not be aimed at ignoring the existing data and claiming that we do not know if thrombolytic treatment is effective or that thrombolytic treatment effect outweighs the risks. The data are clear on the points of efficacy and safety. The real questions worthy of our Society are how we train this and the next generation of emergency physicians to recognize acute stroke, how to implement systems to ensure that appropriate patients receive proven therapy, and how we advance the treatment of patients with this devastating disease, which remains the third leading cause of death in our country. We agree that improving early recognition, public education, and further delineating which patients are most likely to benefit from any early stroke intervention remain formidable tasks. We agree that present and future investigations should be focused on improving the safety of any acute stroke treatment and looking for newer, safer therapies and better prevention. We agree that coordinated stroke care and access to neurologic expertise is optimal, but the fact remains that we do have a proven, effective therapy for acute ischemic stroke with a magnitude of effect much greater than that of thrombolytic therapy for myocardial infarction (11% absolute benefit vs. 3% absolute benefit). We would suggest that SAEM get above the fray, and focus on the academic questions and data regarding acute stroke care in a way that can stimulate our membership to be on the forefront of acute stroke interventions.—**Edward Jauch, MS, MD** (jauchec@ucmail.uc.edu), *University of Cincinnati College of Medicine, Cincinnati, OH, on behalf of the SAEM Neurologic Emergencies Interest Group*  
doi:10.1197/S1069-6563(03)00602-X

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*In reply:*—The stroke position statement has created a strong reaction among many experts devoted to neurosciences research in neurologic emergencies. The SAEM Board of Directors understands the response and wishes to ensure that the statement is not misunderstood. The statement reflects a current reality, however unfortunate, that leaves many stroke victims receiving less than ideal care. The Board also notes the need to address scientific questions of effectiveness, not just efficacy, and anticipates that these will continue to be addressed. The Board does not suggest that the current reality is the ideal or static state.

The Board strongly agrees that the existing reality must be advanced. It should be noted that the Board looks to SAEM members devoted to neuroscience research to lead the advances. It is the job of the Board to take positions, make statements, and note the realities of the academic emergency medicine community so that emerging evidence is implemented realistically and aggressively, but prudently.

## Balancing the Yeses and Nos

*To the Editor:*—I've just gotten around to reading your commentary on "Filtering out the Noise," which I enjoyed.<sup>1</sup> I would add that selective "nos" might make one's domestic life more tranquil and might even decrease so-called "burnout." However, like a reformed alcoholic, I always dreamed of the opportunity lying in wait over the next hill and said "yes" more than I should have. That wisdom being exhibited in retrospect, I might add.

As a teacher (for most of my career), the puzzle is to find the key for each student that piques his or her interest, opens up curiosity, and encourages learning. Although we call ourselves "teachers," we really are trying to facilitate someone else to learn. Teacher of the year is all too often entertainer of the year. Teachers who irritate, who berate, and who oppress are sometimes the ones who, in later years, cause one to say, . . . . "He or she made us learn." The elements of good teaching are highly variable, personal, and hard to put into a formula.

Our Department of Anesthesiology in Miami held an annual weekend "retreat" in which we attempted to address either teaching, research, or clinical care—the three legs on the academic stool! Our faculty numbered about 30 at the time. At one of these retreats, the chairman allowed me to engage in an experiment in which I asked the faculty to put down in one word what their 10- to 12-year-old child would answer if asked by a new neighbor about their occupation? I received about 20 "doctor," another six or seven "anesthesiologist," and only one or two "teacher." As clinicians and researchers, we seemed to downplay or be ashamed of the title of teacher. Why?

The Board believes that the field is in the midst of substantial breakthroughs. Treatment for acute stroke is, and should remain, one of the priority areas for emergency medicine research. Attempts to advance the science and apply it to the typical emergency department, however, must account for current circumstances throughout most of the U.S. health care systems in general and the emergency departments in particular. The Board hopes for, and will continue to support, funded stroke research, particularly efforts to identify safe and effective means of applying promising care. We are proud of the SAEM members devoted to this work. The field is dynamic, and so too are anticipated board statements. The Board looks forward to further dialogue regarding how best to assist in advancing the efforts. The SAEM Board will do whatever is within its power to promote research into neurologic emergencies and improvements in clinical practice. This must remain one of the highest priorities of the specialty.—**Donald M. Yealy, MD** (yealydm@upmc.edu), *Department of Emergency Medicine, University of Pittsburgh, Pittsburgh, PA, and President, Society for Academic Emergency Medicine;* and **James G. Adams, MD**, *Department of Emergency Medicine, Northwestern University Medical School, Chicago, IL, and Senior Associate Editor, Academic Emergency Medicine, for the SAEM Board of Directors*

doi:10.1197/S1069-6563(03)00603-1

As to saying "yes," that is occasionally all too easy on the way up the academic ladder. Ego makes travel and speaking seem attractive in that early point in our career rather than finishing one's research and publishing the results. Even lower on the priority list are the clinical duties that are so important to the residents and students in learning their clinical responsibilities. The right mix of *yes* and *no* is not so easy to the younger and increasingly successful academician.

At any rate, I greatly enjoy reading *AEM* and *JAMA* as my only foray into present-day medicine and find your journal to be most interesting and informative.—**Eugene Nagel, MD (retired)** (enageldoc911@worldnet.att.net)

doi:10.1197/S1069-6563(03)00604-3

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*In reply:*—Thank you for your comments about our journal, and about my commentary. We can all benefit from the experience of our mentors, and appreciate your challenge to consider more our choices, and be proud of our attempts to teach others to think and learn.—**Michelle H. Biros, MD, MS** (biros001@umn.edu), *Editor in Chief, Academic Emergency Medicine*

doi:10.1197/S1069-6563(03)00677-8

## Biological Fallacy

*To the Editor:*—Aggregated data are bread and butter for economists and sociologists. Epidemiologists also have a long track record of using aggregated data in medical and health research. Snow's analysis of aggregated data linking cholera death rates to sources of drinking water in London in 1854 is probably the most storied epidemiologic study.<sup>1</sup> Ecological analysis, however, has been widely regarded as a category of research that is inherently inferior to studies based on individual-level data, mainly because of the well-known, yet often misplaced, notion of *ecological fallacy*. Generally, *ecological fallacy* refers to the error that may occur when inferences about cause-effect relations at the individual level are made from aggregated data. Causes of this error are multifaceted, including confounding effects of unmeasured variables and nonlinear effects of individual-level factors on disease risk.<sup>2,3</sup> In a recent commentary,<sup>4</sup> Jarjoura discussed the issue of *ecological fallacy* with regard to our study examining the relations between neighborhood characteristics and emergency department visit rates.<sup>5</sup> In this rejoinder, I complement Jarjoura's commentary by first dispelling two misconceptions about ecological analysis and then proposing a supplementary concept, namely, the *biological fallacy*.

The first misconception is that the only value of performing an ecological analysis is to make causal inferences at the individual level (i.e., biological inferences). Indeed, ecological analysis often plays this role in medical and health sciences. For instance, by examining the relationship between per capita alcohol consumption and heart disease death rates in different countries, researchers might infer that drinking behavior is associated with the risk of heart disease at the individual level. This biological inference is based on aggregated data, thus susceptible to *ecological fallacy*. Serving as an explanatory tool for biological inferences, however, is not the only role that an ecological analysis can play in research.<sup>6</sup> Causal models can be constructed at the individual level as well as at the population level.<sup>7,8</sup> If the purpose of the study is to make inferences about effects on group outcome measures such as rates (i.e., ecological inferences), as is the case in our study, the concern of *ecological fallacy* is irrelevant.

Although biological inferences may help establish causal associations between individual characteristics and disease risks, ecological inferences aim to explain the variations of a collective phenomenon across population groups, geographic regions, and time periods. There are many important research questions that require ecological inferences. For instance: Why have the prevalence rates of obesity more than doubled in the past four decades in the United States? And why is emergency department congestion such a severe problem in hospitals serving urban and indigent populations? Individual-level comparisons may reveal variables (e.g., genotype and health insurance status) that predispose some individuals to an increased risk of becoming obese or making an emergency department visit. However, findings from these studies alone are insufficient to explain the temporal trends of obesity prevalence and the geographic variations in emergency department congestion. Answering these questions requires making ecological inferences based on aggregated data.

The second misconception is that contextual analysis can substitute for ecological analysis. This misconception is pervasive among epidemiologists, because contextual analysis is less vulnerable to *ecological fallacy* than ecological analysis. Contextual analysis has the advantage of simultaneously estimating the biological effects of individual- and group-level variables. However, the foundation of contextual analysis is individual-level comparison, i.e., the outcome variable in contextual analysis is measured at the individual level. Group-level variables in contextual analysis provide added explanatory power that is unavailable in traditional individual-level studies, because these group-level variables may account for part of the unexplained variance (i.e., residual error) in the model that includes only individual-level variables. As a refined method, contextual analysis may help scientists make more valid biological inferences. However, it is no substitute for ecological analysis. Although multilevel analysis based on hierarchical modeling can tackle both biological and ecological effects, its utility has not been adequately exploited in public health research because of the computational complexity and interpretive difficulty. To understand the behavior and dynamics of group outcome measures, such as emergency department utilization in a given population, ecological inferences based on analysis of aggregated data are essential. As Durkheim adeptly put over a century ago: "Collective tendencies have an existence of their own," and they are "a function of aggregated characteristics of the society."<sup>9</sup>

*Ecological fallacy* arises when biological inferences are made from aggregated data. Conversely, error also may occur when ecological inferences are made from individual-level data. This type of error is best named *biological fallacy*. The cause of *biological fallacy* is the unattainable assumption that a population is merely the sum of individuals. Making ecological inferences from individual-level data also ignores the unique aspects of group outcome measures and their determinants. The term *biological fallacy* might be new, but similar concepts under different names (e.g., "individualistic fallacy"<sup>10</sup> and "type III error"<sup>11</sup>) have been discussed by other researchers. Lexicologically, *biological fallacy* is a more appropriate term than *ecological fallacy*. Whereas *ecological fallacy* has little to do with ecology or ecologists, *biological fallacy* is an error that is encompassed in the thinking of many biomedical scientists. For instance, in response to the obesity epidemic, researchers are engaged in a race to identify the "responsible" genes; similarly, in the search for solutions to emergency department congestion, researchers have conducted case-control and cohort studies to identify individual "risk factors." These studies contribute to the knowledge base for understanding variations in disease risk and health behavior at the individual level. But explaining variations in health statistics across population groups and geographic regions over time based on these individual markers would risk committing *biological fallacy*.

Ecological studies are an integral part of scientific endeavor. Analysis of aggregated data plays both a complementary role and a unique role in our understanding of human health. *Ecological fallacy* is not necessarily a problem

for all ecological studies. It becomes a concern for bias only when biological inferences are made based on aggregated data. On the other hand, individual-level comparisons are not inherently superior to ecological studies. When ecological inferences are made based on individual data, *biological fallacy* is an issue that must be addressed.—**Guohua Li, MD, DrPH** (ghli@jhmi.edu), *Department of Emergency Medicine, Johns Hopkins University School of Medicine, Baltimore, MD*  
doi:10.1197/S1069-6563(03)00597-9

This work was supported by Grants R01AA09963 and R01AG13642 from the National Institutes of Health.

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*In reply:*—I agree with Professor Li about the potential importance of ecological data for identifying contextual effects, and that the role of ecological studies should not be viewed as a crude method of obtaining individual-level inference. He and I disagree, I believe, on how critical cross-level bias can be when inferring contextual effects from ecological associations, and on how potentially valuable multilevel analysis can be for disentangling individual-level from contextual-level effects. It is mathematically and intuitively clear that an association found with aggregated data can be strongly influenced by individual-level effects.<sup>1</sup> For example, an individual's lack of health insurance can influence his or her decision to visit an emergency department (ED). An ecological association found between the crime rates of neighborhoods and general ED visit rates can partly be explained by an association between the crime rates and the proportions with health insurance across neighborhoods. Interpreting such an ecological association without considering the impact on the association of fundamental individual-level variables can result in an ambiguity that may hamper decisions about how best to intervene with problems such as ED congestion or inappropriate ED use. The ambiguity inherent in any observational study (ecological, individual, or multilevel) implies that problems such as ED congestion must be solved, ultimately, by testing interventions in comparative studies. Just as we require a high level of evidence for selecting medical interventions, we also should require a high level of evidence for adopting healthcare delivery interventions.—**David Jarjoura, PhD** (djarj@neucom.edu), *Office of Biostatistics, Northeastern Ohio Universities College of Medicine, Rootstown, OH*  
doi:10.1197/S1069-6563(03)00598-0

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