

COMMENTS AND RESPONSES

Travel-Associated Zika Virus Disease

TO THE EDITOR: Hamer and colleagues (1) provide informative data on the clinical manifestations and epidemiology of Zika virus infection in travelers returning from countries with ongoing viral transmission. Ninety-three cases of Zika virus infection were reported from 63 travel clinics in 30 countries in the GeoSentinel network. Among the reported cases, 4 pregnant women were infected and 3 developed severe fetal complications. The authors note the importance of counseling travelers before departure on measures to prevent sexual transmission of this virus.

All pregnant women with a history of travel in an area of ongoing transmission during their current pregnancy regardless of whether they are symptomatic and all exposed partners of pregnant women should be tested for Zika virus. In addition, we have implemented an algorithm that includes testing all partners of women with a planned pregnancy who may have been exposed to Zika virus. From 2 February to 31 October 2016, a total of 199 women with ongoing or planned pregnancy were tested for Zika virus; 87 partners (43.7%) were counseled and analyzed. Although none of the women had Zika virus infection, 2 partners tested positive by both reverse transcription polymerase chain reaction and serologic testing. One partner of a woman planning pregnancy was symptomatic, and the partner of a woman who was 7 weeks pregnant was paucisymptomatic. Zika virus was detected by reverse transcription polymerase chain reaction testing in the seminal fluid of the 2 positive partners up to 4 months after symptom onset.

Our expanded testing strategy allowed for the diagnosis of 2 additional cases of Zika virus infection that would have been missed because symptoms were absent or mild. The prolonged viral shedding in the semen of partners of Zika virus-negative women who are pregnant or plan to become so highlights the important role of testing partners to prevent possible sexual transmission (2). As with other sexually transmitted infections, family planning services in areas with no ongoing transmission of Zika virus should evaluate its inclusion in the epidemiologic and virologic risk assessment of couples with a history of travel in areas with ongoing transmission.

Giuseppina Liuzzi, MD, PhD

Concetta Castilletti, PhD

National Institute for Infectious Diseases INMI "L. Spallanzani"
Rome, Italy

Francesco Vairo, MD

National Institute for Infectious Diseases INMI "L. Spallanzani"
and Regional Service for Infectious Diseases Surveillance,
Control and Response (SERESMI)
Rome, Italy

Emanuele Nicastrì, MD, PhD

Giuseppe Ippolito, MD

National Institute for Infectious Diseases INMI "L. Spallanzani"
Rome, Italy

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IN RESPONSE: We appreciate Dr. Liuzzi and colleagues' positive feedback on our article, which summarized Zika virus infections reported to GeoSentinel during the first months of the outbreak in the Americas. They describe the results from their screening algorithm for testing women who are planning to conceive or are already pregnant and their sexual partners after travel to an area with risk for this virus even when those partners are asymptomatic. Sexual transmission of Zika virus has been well-established, including transmission from asymptomatic men to their female partners (1). Furthermore, Zika virus RNA has been detected in semen for up to 188 days after symptom onset (2).

The Centers for Disease Control and Prevention recommends Zika virus testing for all pregnant women and symptomatic nonpregnant persons with possible exposure in a country with recent introduction of Zika virus (3). The type of testing varies depending on the time of evaluation relative to symptom onset/possible exposure and the circumstances of possible exposure. Testing is not recommended for asymptomatic couples attempting to conceive in which 1 or both partners have had possible exposure, because a negative test result could be falsely reassuring. Zika virus RNA can remain in semen longer than in blood; as a result, someone with negative results on a blood test could still shed Zika virus in genital secretions (1). If the goal is to reassure couples that unprotected sexual activity is safe after travel to an area with risk for Zika virus infection, screening would require a highly sensitive test with good negative predictive value. However, the current assays pose many challenges related to sensitivity, specificity, and potentially cross-reacting flaviviruses (4, 5). Laboratory capacity and availability of diagnostic supplies and technology can also be problematic in some settings.

Before couples attempt conception, the Centers for Disease Control and Prevention and the World Health Organization recommend abstinence or condom use for men and women for varying durations after symptom onset or last possible exposure to prevent transmission in the periconceptional period. Sexual partners of pregnant women who have possible Zika virus exposure are advised to abstain or use condoms during pregnancy (3). We hope that validated as-

says that can test reproductive tissues (such as semen) will be available soon to allow accurate risk assessment when a prolonged delay of conception is impractical. Such assays would go a long way toward helping to prevent the tragic consequences of congenital Zika syndrome.

Davidson H. Hamer, MD
Boston University School of Public Health
Boston, Massachusetts

Lin H. Chen, MD
Mount Auburn Hospital
Cambridge, Massachusetts

Michael Libman, MD
McGill University
Montreal, Quebec, Canada

Martin P. Grobusch, MD, PhD
University of Amsterdam
Amsterdam, the Netherlands

Douglas H. Esposito, MD, MPH
Centers for Disease Control and Prevention
Atlanta, Georgia

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Heterogeneity in Treatment Effects

TO THE EDITOR: Davidoff's essay (1) on the challenge of heterogeneity in treatment effects is a timely reminder that most clinical trials indicating overall benefit may also be interpreted as merely indicating some efficacy with some patients some of

the time (2). The author rightly focuses on recent work showing how risk stratification can help cut through this heterogeneity to identify broad subgroups of patients likely to benefit from a treatment (3). However, the effectiveness of risk stratification in achieving the ultimate goal—identifying the appropriate treatment for a specific patient—remains unclear. At present, *n*-of-1 trials remain the only means of accomplishing this goal; nevertheless, their use remains limited, not least because of the time and resources required (4).

While we await further methodologic advances, risk stratification may help improve the efficiency of *n*-of-1 trials. The outcome of the risk-stratification analysis of a clinical trial can provide prior insight for a Bayesian analysis of subsequent *n*-of-1 trials. Making the most of evidence from both sources will likely considerably shorten the time needed to reach a decision about treatment and make *n*-of-1 trials more attractive to physicians and patients alike. That phenomenon, in turn, opens up the prospect of a virtuous cycle in which the growing numbers of such trials are aggregated, providing further insight into treatment effects at the population level (5).

Robert A.J. Matthews, MA(Oxon)
Aston University
Birmingham, United Kingdom

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IN RESPONSE: Clinical researchers routinely obtain data from entire heterogeneous trial populations to establish whether specific treatments actually can work, not just seem to do so. But, as Mr. Matthews succinctly notes, careful examination of individual-patient data from many large trials reveals that only some treated patients in such trials actually do benefit from treatment, some of the time (1). Unfortunately, researchers generally remain blind to this very real and substantial heterogeneity in treatment effects and therefore only rarely use trial data to establish whether the treatment they are studying really does (or does not) work in specific patients—even

though clinicians and patients would find such knowledge extremely useful.

This widespread blindness to heterogeneity in treatment effects contributes to at least 3 major undesirable outcomes. First, when some patients in a trial truly benefit from a treatment but do so in numbers too small to generate a meaningful statistical signal of efficacy, the treatment is wrongly written off as being entirely ineffective. In this case, valuable (positive) subgroup-specific treatment information is being wasted, which deprives specific patients of future treatment benefit.

Second, and conversely, when a substantial proportion of patients in a trial truly does not benefit from treatment, as is clearly the case in many trials (1), the results of that trial are correctly interpreted to mean that the treatment *can* work—but only, of course, if the proportion of participants that *does* benefit from treatment in that particular trial is large enough to make the benefit statistically detectable. In this case, valuable (negative) subgroup-specific treatment information is being wasted, which allows future patients to be exposed unnecessarily to treatment-related harm and cost even though they receive little or no benefit from the treatment in question.

Third, the degree of baseline prognostic heterogeneity among trial participants (that is, if they had remained untreated) undoubtedly differs across independent randomized trials of the same treatment. Because baseline prognostic risk is a key determinant of therapeutic effectiveness, these trial-to-trial differences in the mix of baseline prognostic outlook—which generally remain undetected—could therefore account for many of the observed but unexplained differences in *overall* treatment outcome seen across independent randomized trials of the same therapy (2). In this case, valuable information about intertrial differences in heterogeneity in treatment effects is being wasted, which results in unnecessary ambiguity in the entire body of published knowledge about whether a particular treatment can truly provide therapeutic benefit.

Mr. Matthews is right in principle to argue that a formal *n*-of-1 trial is currently the most accurate and reliable way to know whether a treatment actually does work in a specific patient (3). He is also likely right in his innovative assertion that a priori knowledge (from risk-stratified, randomized controlled trials, for example) about which patient subgroups are and are not likely to benefit from a treatment could help clinicians and their patients decide whether even to undertake an *n*-of-1 trial (which can be a sizeable challenge in a busy practice) and interpret its results if they do. The reality, unfortunately, is that medical students and residents currently receive virtually no training or experience in the conduct of such trials; widespread use of this important but much-neglected source of information will not happen anytime soon. That said, clinicians and patients would be grateful to receive—at any time and from any reliable source—accurate knowledge about heterogeneity in treatment effects, especially if that knowledge helps them carry out traditional informal therapeutic trials more efficiently and effectively in everyday practice.

Frank Davidoff, MD

Geisel School of Medicine at Dartmouth College
Hanover, New Hampshire

Annals.org

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Brain-Type Natriuretic Peptide and Amino-Terminal Pro-Brain-Type Natriuretic Peptide Discharge Thresholds for Acute Decompensated Heart Failure

TO THE EDITOR: McQuade and colleagues (1) suggest that achieving predischarge natriuretic peptide (NP) thresholds is associated with reduced heart failure mortality and readmissions. Although this proposed association has biological plausibility, it should be evaluated with caution. One suspects that clinicians would hesitate to discharge patients who seem clinically unstable even if their NP level had decreased. As a result, patients would tend to remain hospitalized longer if their discharge was contingent on achieving both the clinical appearance of stability and a decreasing NP level rather than solely the former. A longer hospital stay in turn would mean that an early relapse would translate into a complicated, prolonged hospitalization rather than a readmission or an early outpatient death. As such, knowing whether the proposed association between a decreasing NP level and better outpatient outcomes persists even after controlling for length of stay would be of interest.

Neil J. Nusbaum, JD, MD

West Texas VA Health Care System
Big Spring, Texas

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IN RESPONSE: Dr. Nusbaum raises an important point about the association between hospital length of stay and readmission rates for patients admitted with acute decompensated heart failure and how this association may have affected our results. In our review, 4 studies adjusted for length of stay in their multivariable analyses (Appendix Table 2 of our article). The association between achieving goal NP levels at discharge and improved readmission and mortality measures was stable despite these adjustments. Results ranged from a hazard ratio of 0.12 (95% CI, 0.02 to 0.72) for mortality to 0.25 (CI, 0.09 to 0.69) and 0.43 (CI, 0.22 to 0.84) for a composite of mortality and readmission for achieving a brain-type NP threshold to 0.64 (CI, 0.44 to 0.93) for a composite outcome for achieving an amino-terminal pro-brain-type NP threshold (Figures 2 and 3 of our article).

Five studies in our review (1–5) reported length of stay for each of their comparison groups, although many did not adjust for this variable in their analyses. In 3 of those studies (3–5), patients discharged with longer lengths of stay were actually less likely to achieve discharge NP goals. These patients likely had either more severe heart failure at baseline with intrinsically higher euvolemic (“dry”) NP levels or more severe initial decompensation but were still undertreated at discharge.

Casey N. McQuade, MD
University of Pittsburgh Medical Center
Pittsburgh, Pennsylvania

Craig A. Umscheid, MD, MSCE
University of Pennsylvania
Philadelphia, Pennsylvania

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OBSERVATIONS

Limitations of Administrative Data for Studying Patients Hospitalized With Heart Failure

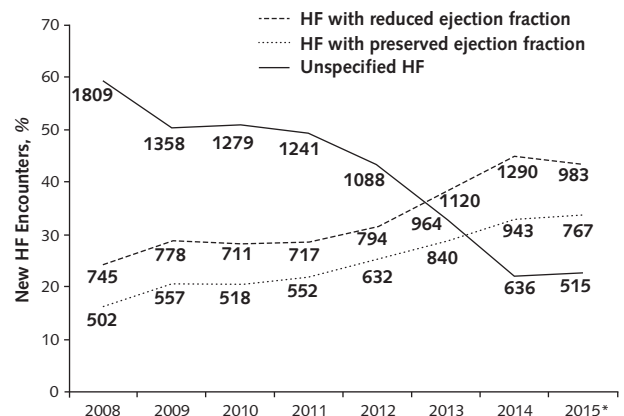
Background: Investigators often use diagnosis codes in administrative databases to identify cohorts of patients, because these databases provide powerful sources of information for exploring epidemiologic trends, synthesizing hypotheses, and studying uncommon diseases (1). Some investigators assume that these codes are accurate, which may explain the inconsistent results between some studies.

Objective: To determine whether the codes that hospitals assign to patients with heart failure change over time.

Methods and Findings: We conducted a retrospective, observational study that included patients of all payers in our large, multisite health care system. We included only 1 encounter per patient. We identified each encounter from January 2008 through September 2015 that was assigned a heart failure code from the International Classification of Diseases, Ninth Revision, Clinical Modification. We further classified these encounters into heart failure with reduced ejection fraction (codes 428.1, 428.2, and 428.4), heart failure with preserved ejection fraction (428.3), and heart failure of unspecified type (428.0 and 428.9). We also compared types of heart failure based on these codes with measures of ejection fraction from the closest echocardiography to the encounter date. The study was approved by the quality improvement committee. All statistical analyses were performed using SAS, version 9.4 (SAS Institute).

We identified 21 339 unique encounters for heart failure. Of these, 7138 (33.5%) were coded as heart failure with reduced ejection fraction, 5311 (25.0%) as heart failure with preserved ejection fraction, and 8890 (41.5%) as heart failure of unspecified type. During the study period, encounters for heart failure of unspecified type decreased from 59.2% to 22.7%, whereas there were increases in encounters for heart failure with preserved ejection fraction (from 16.4% to 33.8%) and heart failure with reduced ejection fraction (from 24.4% to 43.5%) (Figure). Of the encounters coded as heart failure with

Figure. Trends of unique HF encounters, 2008–2015.



HF = heart failure.

* Data cut off at 30 September 2015.

preserved ejection fraction, 3785 had a measured ejection fraction; 16% of these had an ejection fraction less than 50%. Of the encounters coded as heart failure with reduced ejection fraction, 4887 had a measured ejection fraction; 21% of these had an ejection fraction of 50% or higher. The discrepancies between the code for the type of heart failure and measured ejection fraction persisted over time at approximately the same percentages.

Discussion: Over 7 years, the codes given to hospitalized patients with heart failure in this health system shifted from heart failure of unspecified type toward heart failure with reduced and preserved ejection fraction. This shift suggests that coding became more precise, specific, and accurate but also indicates that investigators who use these data should examine them for temporal consistency and clinical validity. For example, 2 studies from 2016 used similar data to calculate frequencies of heart failure in hospitalized patients without the safeguards that we believe are necessary (2, 3).

We recognize that not all the ejection fractions in our study were measured at the same time that heart failure codes were assigned; therefore, some of the discrepancies that we documented do not indicate errors in code assignment. However, we believe that the prevalence of these discrepancies should encourage investigators to address the possibility of coding errors when they use administrative databases in their studies.

Ahmad Masri, MD
Andrew D. Althouse, PhD
University of Pittsburgh Medical Center
Pittsburgh, Pennsylvania

Jeffrey McKibben, BSBA
UPMC Health Services Division
Pittsburgh, Pennsylvania

Joon S. Lee, MD
University of Pittsburgh Medical Center
Pittsburgh, Pennsylvania

Suresh R. Mulukutla, MD
University of Pittsburgh Medical Center and VA Pittsburgh
Healthcare System
Pittsburgh, Pennsylvania

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Normal-Weight Central Obesity and Risk for Mortality

Background: The association between obesity, defined in terms of body mass index (BMI), and mortality in the general population has been controversial (1). Various studies have examined whether central obesity has greater predictive utility than BMI. In a 2015 study of 15 184 adults, paradoxical results suggested that centrally obese participants defined as normal weight on the basis of BMI had the worst long-term survival even when compared with their overweight and obese counterparts (2).

Objective: To replicate these analyses in a larger sample of adults in the general population.

Methods: Participants were recruited from 10 survey years of the Health Survey for England and the Scottish Health Survey, which use a complex survey design (3). Local research ethics committees approved each survey, and all participants gave written informed consent. Trained interviewers measured height and weight to derive BMI, which was categorized as normal weight (BMI of 18.50 to 24.99 kg/m²), overweight (BMI of 25.00 to 29.99 kg/m²), and obese (BMI ≥30.00 kg/m²). Underweight participants (BMI <18.50 kg/m²) and those who died in the first 2 years were excluded as in previous studies to avoid reverse causation (2). Measuring tape was used to record 2 measurements of waist circumference midway between the iliac crest and lower rib, and hip circumference around the widest portion of the buttocks. Central obesity was defined using the World Health Organization criteria of a waist-to-hip ratio of 0.85 or higher in women and 0.90 or higher in men.

Data from individual participants were linked with those from the British National Health Service Central Register to record mortality. Data for survivors were censored to the end of 2009 for the Scottish Health Survey or the first quarter of 2011 for the Health Survey for England. Cox proportional hazards models were used to estimate associations of central obesity with mortality stratified by BMI categories. Models were adjusted for age, sex, smoking status, physical activity, and social occupational class. Variables lying on the causal pathway, such as chronic diseases, were not included as covariates (1, 2). All analyses were performed using SPSS, version 22 (IBM).

Results: The sample comprised 42 702 participants (mean age, 57.7 years [SD, 11.9]; 46.8% men). The prevalence of overweight and obesity assessed from BMI was 43.7% and 25.0%, respectively, and that of central obesity was 53.4%. The prevalence of central obesity across BMI categories was 28.7%, 60.2%, and 72.7% in normal-weight, overweight, and obese participants, respectively.

A total of 5355 participants died over 383 542 person-years of follow-up. Compared with normal-weight participants without central obesity (reference), only normal-weight and obese participants with central obesity were at increased risk for mortality (Table). We conducted several pairwise compar-

Table. Association of Combinations of Body Mass Index Categories and Central Obesity With Mortality

Groups Stratified by Body Mass Index and Waist-to-Hip Ratio	Participants, <i>n</i>	All Deaths, <i>n</i> *	HR (95% CI) for All-Cause Death†	CVD Deaths, <i>n</i>	HR (95% CI) for CVD Death†
Normal weight without central obesity	9560	1064	1.00 (reference)	289	1.00 (reference)
Normal weight with central obesity	3843	744	1.22 (1.11–1.35)	214	1.25 (1.04–1.50)
Overweight without central obesity	7425	703	0.89 (0.81–0.98)	208	0.98 (0.82–1.15)
Overweight with central obesity	11 216	1616	1.00 (0.92–1.08)	569	1.26 (1.09–1.46)
Obese without central obesity	2908	290	0.91 (0.80–1.04)	88	1.05 (0.82–1.33)
Obese with central obesity	7750	938	1.13 (1.03–1.23)	352	1.56 (1.33–1.83)

CVD = cardiovascular disease; HR = hazard ratio.

* Deaths in the first 2 y of follow-up were excluded to prevent reverse causation.

† Adjusted for age, sex, smoking status, physical activity, and social occupational class. Analyses account for the complex sampling design. At the first stage, a random sample of primary sampling units, based on postcode sectors, was selected. At the second stage, a random sample of a fixed number of addresses from the Postcode Address File was then drawn for each primary sampling unit (3).

isons; compared with overweight participants without central obesity (reference), their counterparts with central obesity were at increased risk for mortality (hazard ratio, 1.11 [95% CI, 1.01 to 1.23]). Compared with obese participants without central obesity (reference), their counterparts with central obesity were also at increased risk for mortality (hazard ratio, 1.27 [CI, 1.09 to 1.47]). A total of 1720 participants died of cardiovascular disease; compared with normal-weight participants without central obesity (reference), all participants with central obesity were at increased risk for death from cardiovascular disease (Table). Results were similar when men and women were analyzed separately.

Discussion: We aimed to replicate findings that suggested that centrally obese participants with a normal BMI had the worst long-term survival (2). Our results are partly consistent with these data when examining all-cause mortality but less so for mortality from cardiovascular disease.

Explaining these paradoxical findings in overweight and obese persons, even in the presence of central obesity, is challenging. One possibility is that overweight and obese persons have greater amounts of subcutaneous fat in the hips and legs—that is, fat linked to healthier metabolic profiles. However, longer durations of obesity are associated with increased morbidity (4) and our study relied on anthropometric data collected from a single clinical assessment. Weight histories might have been more informative.

Mark Hamer, PhD

Gary O'Donovan, PhD

David Stensel, PhD

Loughborough University

Loughborough, United Kingdom

Emmanuel Stamatakis, PhD

University of Sydney

Sydney, Australia

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Epinephrine Concentrations in EpiPens After the Expiration Date

Background: Interest and outrage have been mounting over dramatic price increases for the emergency-use epinephrine autoinjection device EpiPen (Mylan). Since 2007, the price of this potentially lifesaving medication has risen more than 400%. This sharp increase has caused patients to ask health care practitioners whether they can use expired EpiPens because they cannot afford to replace them.

Objective: To determine whether EpiPens expired up to 50 months retain their stated potency.

Methods: Over 2 weeks, patients and practitioners at a community clinic were asked to provide unused, expired EpiPens. All pens were examined for color changes and expiration date. Two separate aliquots of each EpiPen's content were quantitatively analyzed for epinephrine concentrations by liquid chromatography (Agilent 1260 Infinity II LC, Agilent Technologies)-tandem mass spectrometry (Triple Quad 5500, AB SCIEX). Epinephrine was monitored using 2 transitions (mass-charge ratio, 184.1 to 107.0 and 184.1 to 166.0) and quantified by isotope dilution using epinephrine-d₆ as an internal standard.

Results: We collected and analyzed 31 expired EpiPens (epinephrine, 1 mg/mL) and 9 EpiPen Jrs (epinephrine, 0.5 mg/mL) (Table). None was discolored. All were 1 to 50 months past their expiration dates. Nineteen of the EpiPens

(61%) and 5 of the EpiPen Jrs (56%) contained at least 90% of their stated amount of epinephrine.

Discussion: Studies have shown that many medications retain full potency up to 40 years beyond their expiration dates (1). However, these studies rarely involve biological agents like epinephrine, which may not maintain their activity as long as other medications. Although medications in the United States are typically assigned expiration dates up to 3 years after manufacture, EpiPens are typically labeled with an expiration date of 18 months or less. One study found that expired EpiPens retained at least 50% of their stated amount of epinephrine up to 90 months past expiration (2), and another found that those less than 25 months past expiration contained at least 90% of the labeled amount (3).

The U.S. Food and Drug Administration permits most medications marketed in the United States to contain 90% to 110% of the labeled concentration of the active ingredients (4). In this study, approximately two thirds of the expired EpiPens and more than half of the expired EpiPen Jrs met this standard and all contained at least of 80% of their labeled concentrations. These findings are important because dosing recommendations for out-of-hospital treatment of anaphylaxis, which are based on anecdotal experience, specify a maximum initial dose of 0.2 to 0.5 mg in adults and 0.01 mg/kg of body weight (with a maximum total dose of 0.3 mg/kg) in children (5). Given that each EpiPen and EpiPen Jr delivers a dose of 3 mL, all of the products tested should deliver a dose within the recommended initial range.

In summary, our data show that EpiPen products can retain substantial amounts of epinephrine well beyond their expiration dates. Although we observed declining concentrations of epinephrine over time, we expect that the dose available 50 months after expiration would still provide a beneficial pharmacologic response. Thus we conclude that the process for establishing expiration dates for EpiPens should be revised and that, in the setting of outpatient anaphylaxis without other therapeutic alternatives, patients and caregivers should consider the potential benefits of using an expired EpiPen.

F. Lee Cantrell, PharmD
California Poison Control System
San Diego, California

Patricia Cantrell, MD
Kaiser Permanente
San Diego, California

Anita Wen, BS
Roy Gerona, PhD
University of California, San Francisco
San Francisco, California

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Table. Total Amount of Epinephrine Remaining in Expired EpiPens

Identification	Dose, mg/mL	Time Beyond Expiration, mo	Epinephrine Remaining, %
EpiPens			
1	1	50	84
2	1	50	88
3	1	49	84
4	1	49	86
5	1	49	87
6	1	49	87
7	1	44	88
8	1	44	90
9	1	36	88
10	1	36	87
11	1	35	86
12	1	35	88
13	1	29	90
14	1	25	91
15	1	25	94
16	1	25	90
17	1	25	90
18	1	23	92
19	1	23	90
20	1	23	92
21	1	23	93
22	1	20	91
23	1	20	92
24	1	13	94
25	1	13	90
26	1	13	95
27	1	13	90
28	1	5	94
29	1	5	89
30	1	5	92
31	1	5	100
EpiPen Jrs			
1	0.5	30	82
2	0.5	30	81
3	0.5	30	86
4	0.5	7	91
5	0.5	7	88
6	0.5	2	97
7	0.5	2	98
8	0.5	1	92
9	0.5	1	99

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CORRECTIONS

Correction: In the Clinic: Atrial Fibrillation

A recent In the Clinic (1) contains an error regarding the administration of apixaban dosing. Table 4, Non–Vitamin K-Dependent Anticoagulation Medications for Atrial Fibrillation, incorrectly states that the apixaban dose should be 2.5 mg twice daily in patients with ≥ 2 of the following: age > 80 y, ≥ 60 kg, creatinine ≥ 1.5 mg/dL. However, that dose should be applied in patients with at least 2 of the following: age > 80 y, ≤ 60 kg, creatinine ≥ 1.5 mg/dL.

This has been corrected in the online version.

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Reference

1. Zimetbaum P. In the Clinic: atrial fibrillation. *Ann Intern Med.* 2017;166:ITC33-48. [PMID: 28265666] doi:10.7326/AITC201703070

Correction: The True Effect of Mass Shootings on Americans

In a recent editorial (1), the number of mass shootings was mistakenly converted to “per 100 000 persons.” The sentence should read as follows: “Data collected on public mass shootings by *Mother Jones* magazine reveal a more than 3-fold increase in the number of people shot in these types of shootings between the years in which a federal ban on assault weapons and large-capacity ammunition feeding devices was in place (21.1 victims per year in 1995 to 2004) and the years since the law expired (65.7 victims per year in 2005 to 2016) (2).”

This has been corrected in the online version.

doi:10.7326/L17-0239

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1. Webster DW. The true effect of mass shootings on Americans. *Ann Intern Med.* 2017. [Epub ahead of print] [PMID: 28462426] doi:10.7326/M17-0943
2. Follman M, Aronsen G, Pan D. US mass shootings, 1982-2017: Data from *Mother Jones*' investigation. *Mother Jones.* 8 January 2017. Accessed at www.motherjones.com/politics/2012/12/mass-shootings-mother-jones-full-data on 17 April 2017.

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