Evaluation and Overview of the National Electronic Injury Surveillance System-Cooperative Adverse Drug Event Surveillance Project (NEISS-CADES)

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Background: Adverse drug events (ADEs) are an important cause of patient injury. Although most medications are prescribed and used in the outpatient setting, prevention efforts focus on the inpatient setting, partly because of limited data on outpatient events. We describe and evaluate a new system for surveillance of outpatient ADEs treated in hospital emergency departments (EDs).

Methods: We used guidelines for evaluating public health surveillance systems, developed by the Centers for Disease Control and Prevention, to assess the performance of the National Electronic Injury Surveillance System-Cooperative Adverse Drug Event Surveillance project (NEISS-CADES) from January 1, 2004 through December 31, 2004.

Results: NEISS-CADES is a nationally representative surveillance system that identifies ADEs using ED clinical records. Of 10,383 reports in 2004, 100% listed patient age, sex, and disposition; 98% listed the implicated drugs. A 6-hospital evaluation of data quality, completeness, and other system attributes showed that NEISS-CADES data accurately reflected clinical records with respect to patient age and sex (100%), primary diagnosis (93%), implicated drugs (93%), primary treatments (80%), and diagnostic testing (61%). Sensitivity of case identification was estimated to be at least 0.33; estimated positive predictive value was 0.92. Data collection does not require additional work by clinical staff and has been well accepted by participating institutions.

Conclusions: NEISS-CADES provides detailed and timely information on outpatient ADEs treated in EDs and identifies specific drugs and circumstances associated with these injuries. Findings from NEISS-CADES can help design and prioritize patient safety interventions for outpatient ADEs.

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An adverse drug event (ADE) occurs when a drug intended for therapeutic use has an unintended and injurious effect. In 1999, the Institute of Medicine (IOM) report, *To Err is Human,* identified ADEs as a frequent cause of adverse events that contribute to patient morbidity and death.[1] In 2000, the US General Accounting Office (now the Government Accountability Office) found national ADE surveillance, particularly surveillance for outpatient ADEs, to be insufficient.[2] Despite limited surveillance data, efforts to improve drug safety and prevent ADEs continue, focusing primarily on the safety of hospitalized patients[3–5] and the detection of previously unrecognized adverse effects. Although detecting new drug-related problems is important, the greater public health burden may be from "older drugs, poorly used,"[6] particularly among patients in community settings.[7,8]

In 1971, the Consumer Product Safety Commission (CPSC) instituted the National Electronic Injury Surveillance System (NEISS) to identify and monitor injuries from consumer products for which patients sought emergency department (ED) care.[9] In collaboration with the Centers for Disease Control and Prevention's (CDC) National Center for Injury Prevention and Control, NEISS was expanded in 2000 to collect nationally representative data on all external causes of nonfatal injuries and poisonings, including the adverse effects of drugs that required treatment in EDs.[10] To respond to gaps in national outpatient ADE surveillance, a pilot NEISS project began in 2002 to evaluate the feasibility of collecting detailed information on ADEs.[11] Findings from that study prompted the CDC, CPSC, and the Food and Drug Administration (FDA) to initiate the NEISS-Cooperative Adverse Drug Event Surveillance project (NEISS-CADES) in 2003. NEISS-CADES is used by all 3 agencies to monitor and characterize the public health burden of outpatient ADEs treated in EDs. We present the first comprehensive evaluation of NEISS-CADES as a public health surveillance system.

BACKGROUND

NEISS-CADES conducts active, national surveillance for ADEs treated in EDs. A case in NEISS-CADES is defined as an ED visit for a condition that the treating physician explicitly attributes to the use of a drug or a drug-specific effect. ADEs in NEISS-CADES include immunologically-mediated reactions, adverse effects of medications at recommended doses, accidental ingestions, unintentional overdoses (including those from drug-drug interactions), and secondary effects (eg, choking, injection site infections, hip fracture from a fall due to sedative effects of a medication). Drugs include prescription and over-the-counter medications, vaccines/immunizations, vitamins, dietary supplements, and herbal products. (In its organization, operations, and regulations, the FDA distinguishes drug products from vaccines, vitamins, and dietary supplements. Drugs and vaccines require FDA approval before they can be sold, whereas vitamins and dietary supplements do not.) ED visits attributed to intentional self-harm, drug therapeutic failures, recreational drug use, or drugs administered in the treating ED are excluded.

NEISS-CADEs operates in 63 hospital EDs, selected as a stratified probability sample of all hospitals in the United States and its territories with a minimum of 6 beds and a 24-hour ED.[12,13] The sample includes 4 strata based on hospital size and 1 stratum consisting of children's hospitals. Data are weighted according to the inverse of hospital selection probability in each stratum, adjusted yearly for nonresponse, hospital closure, and hospital merger with other healthcare institutions.[12]

At each participating site, data abstractors employed by CPSC review clinical records of ED visits. Abstractors are instructed to focus on the physician diagnosis section of the clinical records. If a condition is linked to a drug effect in this section, the case is included. If the diagnosis describes a condition that is frequently due to a drug effect (such as rash, bleeding, or hypoglycemia), other sections of the patient chart are examined for evidence of a drug-related injury (eg, instructions to discontinue a medication and avoid future use, documentation of supratherapeutic international normalized ratio in patient on anticoagulants, or documentation of insulin use in a patient with hypoglycemia).

Once an ADE has been identified, abstractors use a computer-based data entry system to record a case report. The data entry form, derived from the MedWatch Form FDA3500,[14] includes fields for recording the name, dose, route, frequency, and duration of use for up to 2 suspected drugs (Fig. 1). Additional information on clinical testing, diagnosis, treatment, and patient disposition is also recorded, and a free-text narrative field is used to describe the circumstances surrounding the injury. Abstractors at participating hospitals receive training on ADE identification and reporting

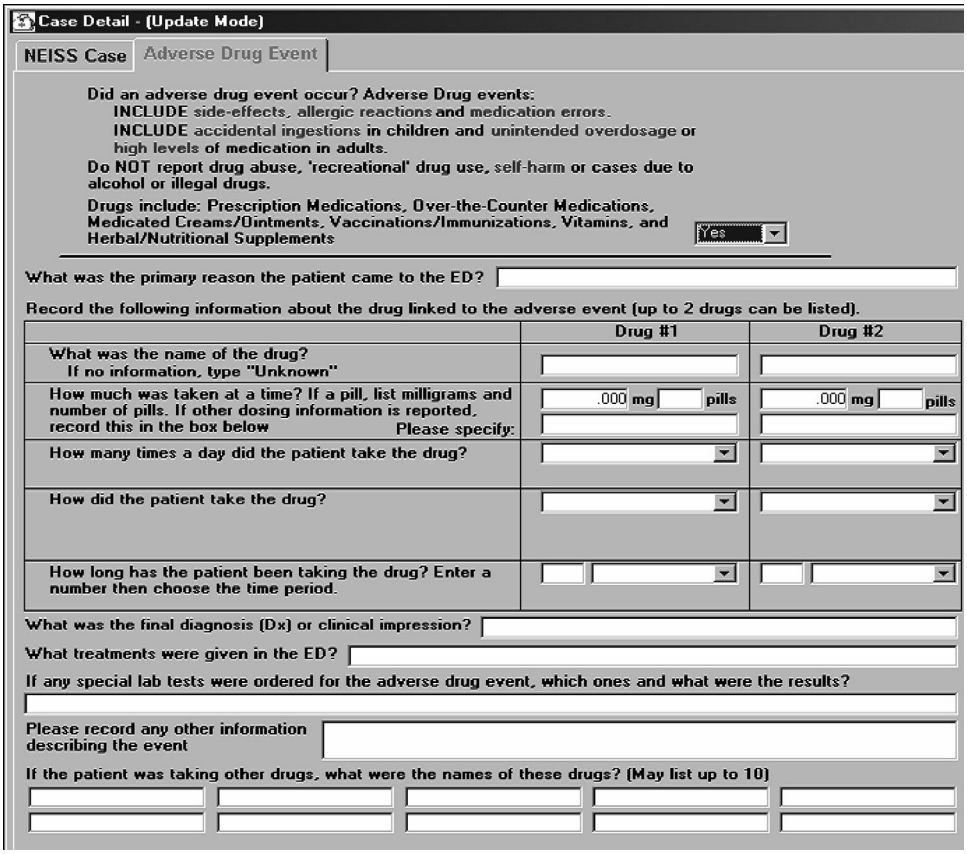

FIGURE 1. Electronic data entry screen, National Electronic Injury Surveillance System-Cooperative Adverse Drug Event Surveillance project (NEISS-CADES).

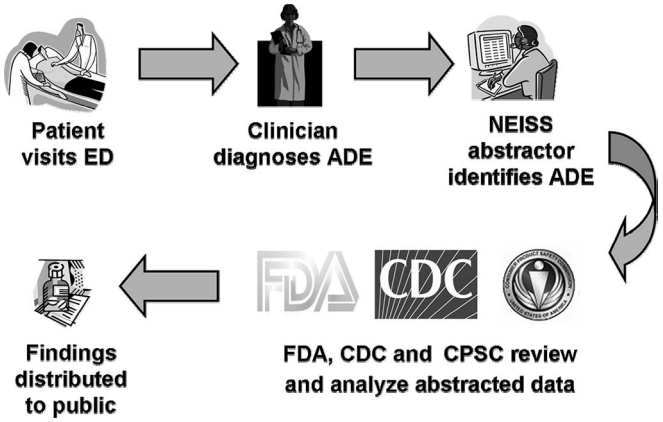

FIGURE 2. Adverse drug event data collection, National Electronic Injury Surveillance System-Cooperative Adverse Drug Event Surveillance project (NEISS-CADES). Surveillance begins with patient presentation at emergency department for treatment of ADE-related symptoms. After collection of data, cases are analyzed by the Centers for Disease Control and Prevention, the Food and Drug Administration, and the Consumer Product Safety Commission before dissemination of results to patients, clinicians, and public health practitioners.

before submitting reports to NEISS-CADES. Training is conducted at CPSC or through distance-based learning sessions and includes specific guidelines and practice exercises. Hospital abstractors also receive updated reference materials, individual evaluations, and periodic site visits to help assure data quality.[10,11]

Case reports are electronically transmitted to CPSC, where an initial quality review is performed (Fig. 2). Deidentified data are then forwarded to CDC where all case reports involving pharmaceutical products are reviewed. Reports which meet the ADE case definition but fail to include complete information are returned to CPSC for investigation and revision. Complete ADE reports are coded by a contractor supervised by FDA and CDC using the Medical Dictionary for Regulatory Activities (MeDRA) to describe the following: diagnoses, symptoms, type of adverse events, and type of medication errors. Implicated drugs are standardized with respect to drug name and then classified using the National Drug File Reference Terminology.[15] CDC, CPSC, and FDA collaborate on final data analyses and dissemination of findings. Participation by hospitals is voluntary and confidentiality of all data is ensured by the Consumer Product Safety Act (15 USC. 2051–2084). Data are collected, managed, analyzed, and interpreted under public health surveillance authority and do not require human subject review or institutional review board approval.

METHODS

We assessed the operation of NEISS-CADES using CDC's 2001 updated guidelines for evaluating public health surveillance systems.[16] These guidelines identify 9 system attributes as criteria by which to evaluate the performance of a surveillance system.

We conducted a qualitative evaluation of 5 attributes (acceptability, flexibility, representativeness, simplicity, and stability) based on the system's design, history, and information from participating institutions and agencies. For the remaining 4 attributes [timeliness, data quality, positive predictive value (PPV), and sensitivity], we analyzed data collected by NEISS-CADES during 2004. We assessed system timeliness by calculating the number of days from date of ED visit to entry of case report into NEISS-CADES. We assessed data completeness, a component of data quality, by calculating the proportion of complete data elements completed by abstractors.

We used data collected from a convenience sample of 6 NEISS-CADES hospitals from January 1, 2004 to June 15, 2004 to evaluate data validity, a second component of data quality, PPV, and system sensitivity.[10] The 6 hospitals were chosen as a convenience sample and were selected to represent a range of ADE reporting (0.2–1.7% of ED visits) and a range of bed sizes (3 very large, 1 large, 1 medium, and 1 small). Large metropolitan (1 hospital), smaller metropolitan (3 hospitals), and rural areas (2 hospitals) and 5 of 9 US census geographic divisions were represented. No pediatric specialty hospital was included in this sample. Two expert reviewers, a physician and a medical epidemiologist with experience in medical record abstraction and ADE surveillance, independently examined all ED medical records from randomly selected days to determine which ED records met the NEISS-CADES case definition. Up to 1200 charts or up to 20 days of charts were retrieved from each hospital. We assessed data validity by comparing data from cases reported by NEISS abstractors in 2004 to findings from expert review to determine abstractor–expert agreement for 9 data fields. Sensitivity and PPV were estimated as previously described.[10,17]

CDC guidelines further indicate that a surveillance system is useful if it satisfactorily addresses at least one of the following outcome-related questions.[12] Can the surveillance system: (1) detect ADEs in a timely way to permit prevention, (2) estimate the magnitude of morbidity and identify associated risk factors, (3) stimulate research leading to prevention, (4) detect trends in ADEs over time, (5) permit assessment of prevention measures, or (6) lead to improved clinical, social or policy practice? We reviewed the application of NEISS-CADES surveillance data to issues of public health importance from 2004 to 2006 for evidence that the system could address these questions.

RESULTS

System Attributes

Information collected for 9 surveillance system attributes provides evidence that 6 attributes are strengths of NEISS-CADES, and 3 are relative limitations of the system (Table 1).

Representativeness

Representativeness refers to the ability of a surveillance system to describe the occurrence of a health-related event (HRE) over time and its distribution in the population by

TABLE 1. Strengths and Limitations of Surveillance Attributes, National Electronic Injury Surveillance System-Cooperative Adverse Drug Event Surveillance Project (NEISS-CADES)*

Surveillance Attribute	Definition	Qualitative Judgment
Acceptability	Willingness to participate in system	Major strengths
Positive predictive value	Proportion of reports that are true cases	
Representativeness	Degree to which population is represented	
Data quality	Data completeness and validity	Relative strengths
Flexibility	Adaptability to changing needs	
Timeliness	Speed between reporting steps	
Sensitivity	Proportion of true cases detected	Limitations
Simplicity	System design and ease of operation	
Stability	Reliability and availability of system	

*Adapted from Centers for Disease Control and Prevention's Updated Guidelines for Evaluating Public Health Surveillance Systems.[16]

place and person.[16] Because NEISS-CADES hospitals are drawn from a nationally representative sample, the population under surveillance for ADEs more closely represents the age, sex, race/ethnicity, education, and socioeconomic status of the entire country than a more narrowly drawn sample chosen for a clinical trial or selected from a single payer's claims database. In addition, the system captures ADEs treated in a wide spectrum of outpatient healthcare settings (eg, EDs in large urban, rural, and children's hospitals), rather than the more homogenous practice environments represented in clinical trials or certain managed care settings. However, because the system operates only in hospital EDs, it will not detect events among people who are treated elsewhere (eg, in other ambulatory care centers or inpatient units in hospitals), or those who do not seek care at all. NEISS-CADES may also preferentially capture ADEs occurring in people more likely to seek care in EDs.

Positive Predictive Value

PPV is defined as the proportion of ADEs reported by NEISS-CADES that are true ADEs.[16] From January 1, 2004 to June 15, 2004, 29 ADE cases were reported by NEISS-CADES surveillance of 4561 ED medical records conducted in the 6-hospital sample. Based on expert review, 25 of 29 cases reported by NEISS-CADES met the case definition; 4 of 29 were judged to be false-positive reports. Median age of these 25 cases was 57 years (range, 19 months–100 years), and 14 of 25 cases (56%) were female. Adjusting for probability of selection, weighted PPV was estimated to be 0.92 [95% confidence interval (CI), 0.85–1.0], indicating that nearly all reported cases were confirmed as ADEs by expert review.

Acceptability

Acceptability reflects the willingness of involved parties to participate in the surveillance system.[16] The administrative requirements and resource expenditures for the healthcare facilities participating in NEISS-CADES are minimal. Hospitals are not required to contribute personnel or infrastructure to support the system, and NEISS abstractors collect medical record data in a minimally obtrusive manner. Furthermore, the system operates without direct involvement from care providers and thereby imposes no additional time or resource demands on clinical staff. One quantitative measure of acceptability for a surveillance system is the rate at which reporting institutions discontinue their participation. To date, no enrolled hospitals have revoked their participation in NEISS-CADES. Finally, because NEISS-CADES leverages resources of an existing surveillance system, the marginal costs of conducting ADE surveillance are small, in comparison to other national surveillance efforts managed by the sponsoring agencies.

Data Quality

Data quality reflects both the completeness and validity of data collected by the surveillance system.[16] In a demonstration project involving 9 NEISS hospitals in 2002, 598 ADEs were reported; completeness for these data ranged from 77% to 100% for key data elements.[11] In 2004, 10,383 ADE cases were reported from all participating hospitals, and completeness for key data elements in 2004 ranged from 82% to 100% (Table 2). In 25 reports of ADEs in 2004, agreement between abstractors and expert reviewers for 2 important data elements, drug identity and patient diagnosis, was 0.93 (Table 3). Less agreement was seen for diagnostic testing (0.61), drug frequency (0.68), and duration of therapy (0.56). Disagreement was due primarily to missing values for cases reported by abstractors, not incorrect data entry.

Flexibility

Flexibility reflects how well the system adapts to changing information needs or operating conditions.[16] NEISS-CADES codes ADE reports using 2 standard vocabularies for electronic health data: MedDRA terminology for medical coding[18–20] and the Veterans Administration National Drug File Reference Terminology (NDF-RT) for drug coding.[21,22] Standardized terminology facilitates comparability and exchange with electronic information from other systems, which enhances system flexibility. Furthermore, because ADE identification in NEISS-CADES is based on the treating physician's clinical diagnosis, a broad and changing range of medication effects can be monitored over time. Thus, newly recognized effects of medications

TABLE 2. Completeness of Patient and Drug Characteristics, National Electronic Injury Surveillance System-Cooperative Adverse Drug Event Surveillance Project (NEISS-CADES), 2004

	N = 10,383	%
Completeness of patient characteristics		
Age	10,383	100
Sex	10,381	100
Disposition	10,383	100
Diagnosis described in ED medical record	10,277	99
Treatment described in ED medical record	9435	91
Diagnostic testing described in ED medical record	8731	84
Race/ethnicity	7842	76
Completeness of drug characteristics		
Identity	10,023	97
Route of administration	8550	82
Frequency	4478	43
Duration of use	4255	41
Dosage	3861	37

TABLE 3. Validity of Patient and Drug Characteristics, National Electronic Injury Surveillance System–Cooperative Adverse Drug Event Surveillance Project (NEISS-CADES), 2004

Data Element	Agreement of NEISS Report and Gold Standard*
Patient age	1.00
Patient sex	1.00
Name of drugs involved	0.93
Primary diagnosis	0.93
Primary drug dose	0.80
Indicated treatments	0.80
Primary drug frequency	0.68
Diagnostic tests ordered	0.61
Primary drug duration of use	0.56

*Agreement between data entry personnel is measured against independent chart review by 2 experts for NEISS-CADES reports of 25 adverse drug events in 2004. A value of 1.00 denotes 100% agreement. Primary diagnosis reflects the diagnosis indicated in the emergency department record; indicated treatments are those given to the patient in the emergency department; diagnostic tests ordered are those conducted in the emergency department; drug frequency and duration of use are based on patient report.

can be captured, as well as known effects of older drugs, without changing the system's case definition or data elements. However, NEISS-CADES functions as a subsystem of the NEISS, and any major modifications, such as increasing the number of participating hospitals, would be subject to surveillance priorities and operating constraints of CPSC.

Timeliness

Timeliness describes the speed between steps in a surveillance system.[16] The speed with which data are available from NEISS-CADES is equivalent or superior to many other surveillance efforts for ADEs. Data are collected from the medical record shortly after the patient's healthcare encounter, and become available for preliminary analysis to address specific public health concerns within 1 month. In 2004, 67% of cases were reported to CPSC within 7 days of the ED visit, and 93% of cases were reported within 30 days. Additional time is required for complete quality review and MedDRA coding of cases, and assignment of sample weights is completed 6 months after the end of each calendar year. Thus, final analyses based on MedDRA coding and computing national estimates may not be performed until that time.

Sensitivity

Sensitivity refers to the proportion of actual events among cases detected by a surveillance system, as well as the ability of the system to monitor changes in incidence of an HRE over time. In 6 NEISS-CADES hospitals from January 1, 2004 through June 15, 2004, 68 ADE cases were identified by expert review, resulting in a weighted sensitivity estimate of 0.33 (95% CI, 0.23–0.44).[10] The most common unreported cases were episodes of bleeding from anticoagulants and hypoglycemia due to insulin; if these cases are excluded, sensitivity improves to 0.45 (95% CI, 0.31–0.59).

Simplicity

Simplicity refers to both a system's structure and its ease of operation.[16] Although the amount of information recorded for each NEISS-CADES case can be extensive, it is acquired from a single source, the patient's ED chart, which minimizes the effort required for data collection. Analysis and interpretation of reports are simplified by the fact that data are collected by professional abstractors with consistent levels of training, infrastructure, and commitment to reporting.

Once data are entered at the collection sites, subsequent processing requires transmission among 3 federal agencies (CPSC, CDC, and FDA) before analysis can be completed. Ensuring integrity while sharing data among the agencies requires strict attention to issues of recoding, duplication, and updating, which add a level of complexity to the system. Finally, although NEISS-CADES uses the same general structure that NEISS has used for years, the additional ADE training required for data coders and managers decreases the system's overall simplicity.

Stability

A system's stability is a function of its ability to operate without interruption and the availability of its information for use by stakeholders.[16] NEISS has been in operation since 1971, and NEISS-CADES is one of several enhancements that have been implemented successfully in the past 30 years. Funding for NEISS-CADES is allocated on a yearly basis.

System Usefulness

We found evidence that NEISS-CADES adequately addresses 2 questions important to system usefulness. First, NEISS-CADES has demonstrated its ability to detect ADEs in time to permit implementation of prevention efforts. In February and March 2006, 2 FDA Drug Safety Advisory Panels addressed the safety of stimulant drugs prescribed for attention deficit hyperactivity disorder (ADHD).[23] The increased interest in ADHD stimulant drug safety prompted an analysis of NEISS-CADES reports of adverse events from

these drugs. We found that an estimated 3075 patients came to EDs in 2004 for adverse events attributed to these medications, and many of these events (45%) were potentially preventable overdoses in children.[24] These results were delivered to patients and clinicians via publication 3 months after the first Advisory Panel meeting.

Second, data from NEISS-CADES have been used to estimate morbidity and identify risk factors associated with ADEs. Estimates from 2004 to 2005 indicate that more than 700,000 patients were treated annually in US emergency departments for ADEs and 1 in 6 were hospitalized. In addition, 3 drugs (insulin, warfarin, and digoxin) were associated with 33% of ADEs in persons age 65 and older.[25] Among children age 18 or younger, accidental overdoses were the most common type of ADEs, and nearly half of ADEs occurred in toddlers age 1–4.[26]

Whether NEISS-CADES can stimulate further research that will prevent ADEs, detect trends over time, permit assessment of prevention measures, or improve public health practice has yet to be determined.

CONCLUSIONS

NEISS-CADES is one of the few sources of nationally representative data on ADEs among outpatient medication users available to public health practitioners. By providing timely and detailed information NEISS-CADES can monitor ADEs in defined patient populations (eg, older adults, children), from specific drugs (eg, antimicrobials, anticoagulants) and that result in specific conditions (eg, anaphylaxis, hypoglycemia). Once common circumstances are identified, intervention strategies can be designed to minimize the incidence and severity of adverse events.

NEISS-CADES has several limitations. First, surveillance is conducted in hospital EDs and does not capture ADEs treated in other healthcare settings (eg, ambulatory clinics, urgent care centers, or private physician's offices). Usefulness of the system is therefore predicated on the assumption that outpatient events treated in hospital EDs describe an important piece of the overall ADE problem. However, nonhospitalized persons with acute, serious ADEs are likely to seek treatment from hospital EDs, and prior studies from single institutions have concluded that ADEs represent an important cause of ED visits.[27,28] Second, polypharmacy can complicate attribution of a patient's clinical symptoms to a single, specific drug. However, NEISS-CADES allows 2 causative drugs to be recorded as structured data elements, and if additional drugs are suspected, this information may be added as a free-text description. Third, ADEs may not be identified by NEISS-CADES unless the treating physician recognizes an association between a drug's effects and a patient's presenting symptoms. Documentation of ADEs in the medical record may be subject to the treating clinician's medical training and experience, the type of drug involved, or individual hospital reporting practices. For example, a physician may be more likely to diagnose an ADE if the event is well established in published literature; rare drug effects may not be noted in patients' charts as frequently. This may be particularly true in EDs where emphasis is often on triage and patient stabilization rather than definitive diagnosis. As a result, NEISS-CADES may be biased toward collecting ADEs that have acute and life-threatening consequences which require immediate treatment (eg, angioedema after ACE inhibitor use), can be readily confirmed by laboratory tests (eg, digoxin toxicity), and have signs and symptoms that are well known in the medical community (eg, rashes associated with antibiotics). Thus, the system functions well as a monitor for common, well-established ADEs but may fail to detect less well-recognized or emerging adverse events. Fourth, a combination of relatively low sensitivity and high PPV in NEISS-CADES suggests that the true number of ADEs may be higher than national estimates calculated from NEISS-CADES data. However, spontaneous or passive reporting systems typically have much lower sensitivity and frequently fail to capture even 10% of ADEs.[29] For example, the FDA maintains the Adverse Event Reporting System (AERS) database, which includes information on ADEs from the MedWatch Program and mandatory submissions from pharmaceutical manufacturers.[14] AERS contains events noted by patients and consumers, as well as healthcare providers, and may include reports that lack clinical evidence linking the event to the reported drug. The sensitivity for AERS, which can vary by type of drug, time since a drug's release, and type of adverse event, ranges between 0.01 and 0.38.[30] Although sensitivity in NEISS-CADES is similarly imperfect, the system can still be useful in monitoring trends in ADEs over time, as long as sensitivity remains reasonably constant over time.[16] Quality assurance and training updates for NEISS coders are part of ongoing efforts to improve sensitivity of ADE identification, and further evaluations are planned. Finally, NEISS-CADES does not provide estimates of drug exposure in the surveillance population. Thus, although the total number of ADEs resulting from a specific drug can be estimated, additional data are needed to calculate the number of ED visits relative to the amount of drug prescribed.

The public health impact of ADEs is substantial, and many ADEs, particularly serious events, are preventable.[31,32] Detailed information on circumstances surrounding ADEs in the outpatient setting can help prevent ADEs by prioritizing interventions and identifying areas for further research. Because public health surveillance systems are designed to be both ongoing and systematic,[33] they can provide evidence on which to base prevention efforts and policy decisions. NEISS-CADES is an effective public health surveillance system that characterizes the burden of outpatient ADEs treated in US emergency departments. Our evaluation indicates that NEISS-CADES provides complete and valid information on key data elements such as patient diagnosis and disposition, and the names and doses of drugs involved in ADEs. The system is well accepted by its participants and provides nationally representative data that have a high predictive positive value. NEISS-CADES addresses a primary outcome of ADEs—manifestation of patient symptoms and subsequent health-seeking behavior—and thereby frames ADE surveillance in the context of traditional public health reporting. NEISS-CADES also collects information on ADEs

resulting from commonly used older drugs, not just newly developed medications, and thus monitors drugs that may have the largest impact on public health.

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