LEADING ARTICLE

Drug Safety 2006; 29 (5): 375-384
0114-5916/06/0005-0375/$39.95/0

Data Mining in the US using the Vaccine Adverse Event Reporting System

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Abstract

The US Vaccine Adverse Event Reporting System (VAERS), which is charged with vigilance for detecting vaccine-related safety issues, faces an increasingly complex immunisation environment. Since 1990, steady increases in vaccine licensing and distribution have resulted in increasing numbers of reports to VAERS. Prominent features of current reports include more routine vaccine co-administration and frequent reports of new postvaccination clinical syndromes. Data-mining methods, based on disproportionality analyses, are one strategy being pursued by VAERS researchers to increase the utility of its complex database. The types of analyses used include proportional reporting ratios, association rule discovery, and various 'historic limits' methods that compare observed versus expected event counts. The use of such strategies in VAERS has been primarily supplemental and retrospective. Signals for inactivated influenza, typhoid and tetanus toxoid-containing vaccines have been successfully identified. Concerns flagged through data mining should always be subject to clinical case review as a first evaluation step. Persistent issues should be subject to formal hypothesis testing in large linked databases or other controlled-study settings.

Automated data-mining techniques for prospective use are currently undergoing development and evaluation within VAERS. Their use (as one signal-detection tool among many) by trained medical evaluators who are aware of system limitations is one legitimate approach to improving the ability of VAERS to generate vaccine-safety hypotheses. Such approaches are needed as more new vaccines continue to be licensed.

1. The US Vaccine Adverse Event Reporting System (VAERS)

The US Vaccine Adverse Event Reporting System (VAERS), which was established in 1990, is jointly operated by the Centers for Disease Control and Prevention (CDC) and the US FDA. As the frontline national passive surveillance system for vaccine safety, VAERS is primarily responsible for detecting rare or novel vaccine adverse events (VAEs) that may require further study. Such signals have typically been detected by review of case reports and case series published in the medical litera-

ture, inquiries from providers and the general public[1] or media attention.[2]

Although VAERS is subject to well described limitations common to other passive surveillance systems,[3] including under-reporting and reporting bias, its monitoring infrastructure successfully detected the signal that associated intussusception with rotavirus vaccine.[4] It has also helped to fully characterise the safety profile of newly licensed vaccines[5,6] and identify risk factors for rare serious adverse reactions to vaccines.[7,8]

2. Current Context of Vaccine-Safety Activities

Since 1999, multiple prominent vaccine-related safety issues have arisen almost simultaneously. These have included the withdrawal of rotavirus vaccine,[9] concerns about the thimerosal content of licensed vaccines, which led to its removal from almost all recommended US childhood vaccines[10] and the now apparently disproved hypothesis that the measles-mumps-rubella (MMR) vaccine was linked to autism.[11]

Additional factors that have increased the visibility of VAERS include the capability for secure electronic reporting,[12] which was implemented in 2002, and the use of VAERS to support the US smallpox vaccination programme from 2003 onward.[13] There has also been increasing scientific, public policy and media scrutiny of postlicensure-safety monitoring for medical products, including specific attention to vaccine-safety activities.[14]

This article will (i) present data that underpins the rationale for the use of data mining in VAERS; (ii) provide an overview of general types of data-mining methods used; (iii) review the objectives of data-mining techniques; and (iv) discuss illustrative examples of how data mining is used to identify and clarify specific safety signals.

3. Increasing Complexity of the VAERS Database

In order to assess time trends in spontaneous vaccine-safety reports in the US relative to measures of vaccine usage, the VAERS team have reviewed recent trends in vaccine licensing and changes in vaccine immunisation schedules. In addition, we were able to describe the changes in complexity of the VAERS database using vaccine-combination and symptom-code data.

Since the inception of VAERS, there has been a three-fold increase in the number of licensed vaccine products in the US. In 1990, there were 16 vaccines under surveillance for safety.[15] In 2004, there were 49 licensed vaccine products.[16]

In 1989, there were eight recommended childhood vaccines.[17] Children received no more than six shots by the time they were 2 years old and not more than two shots at a single visit. Now, children may receive as many as 20 shots by 2 years of age and up to five shots at a single visit.

One relatively crude measure of increased vaccine usage among the total US population is the total number of vaccine doses distributed, which has been gradually but steadily increasing since the mid 1990s (figure 1). In 2003, the total number of vaccine doses distributed was just over 235 million – or nearly one dose per capita.[18]

In parallel with increases in vaccine distribution, there has been an increase in the number of passive surveillance reports received by VAERS over the past 5 years (figure 2). Through end 2003, a total of 162 606 reports had been received.[18] The number of reports involving hospitalisation, death, life-threatening illness or disability (designated as 'serious' by regulatory standards[19]) has also increased since the inception of the VAERS system. Such reports are subject to enhanced follow-up and surveillance analysis.

The number of combination vaccines has increased and the number of potential vaccine permutations that may be given simultaneously has increased significantly. Between 1991 and 2003, the total number of vaccines and vaccine combinations seen in reports to VAERS for both children and adults increased from 101 to 951.[18] Since the inception of the VAERS system, >1000 separate symptoms (reflected as Coding Symbols for Thesaurus of Adverse Reaction Terms [COSTART] codes;[20] VAERS plans to begin use of the Medical Dictionary for Regulatory Activities [MedDRA] system by 2006) have been reported as potential adverse events. This number has increased incrementally but steadily (figure 3). Most reports describe more than a single symptom.

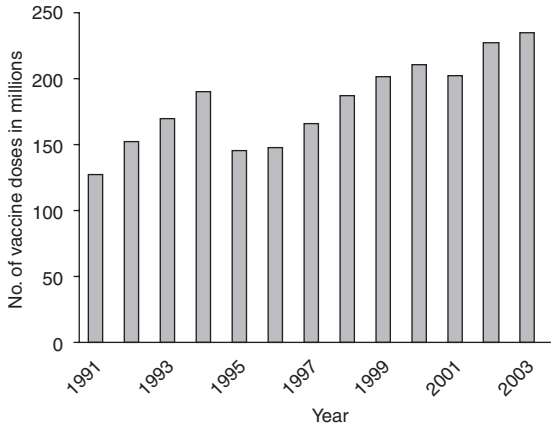

Fig. 1. Number of vaccine doses distributed (in millions) in the US, 1991–2003.[18]

In summary, during the period from 1991 to 2003, the number of licensed vaccines tripled, accompanied by steady proportionate increases in vaccine distribution and spontaneous adverse event reporting (7.0 vs 6.9% annual growth).[18] At the same time, there was a nearly ten-fold increase in the number of potential exposures (vaccine combinations) involved in VAERS reports along with an 8.6% annual increase in the total number of reported symptom codes.[18] However, all possible combinations of vaccines that will be given in practice cannot feasibly be tested in prelicensure studies.[21]

In the near future, it is anticipated that additional vaccines will be licensed and/or recommended for infants, adolescents and adults. Examples include meningococcal conjugate vaccines (MCV), a newly formulated rotavirus vaccine and diphtheria-tetanus-acellular pertussis (Tdap) vaccines designed for use in adolescents and adults.

The disproportionate increases in both vaccine combinations and possible vaccine-associated symptoms reflect the increasing complexity of the VAERS database. Given the possibility of increasing difficulty in detecting vaccine-safety signals, we are actively supporting the use of statistically based 'data-mining' tools to be used in conjunction with traditional case review methods.

4. Data Mining: Background

Data-mining methods for use in pharmacovigilance originated in drug safety,[22,23] which deals with many of the same issues, including multiple exposures and potential outcomes, and very large databases of spontaneous reports. Although it is not universally agreed on, a 'signal' has been defined as "any disproportionate difference in the occurrence of an event in the population of users of a given drug (or class of drugs), or any difference in the rate of reporting of an event in association with a drug relative to other drugs…".[24] The 'signal' concept is closely tied to theoretical underpinnings of data mining. Because disproportionality is inherent to what constitutes a signal, most data-mining methods involve analysis of various types of disproportions within product-safety databases.

Important differences exist between spontaneous reporting databases for drugs and vaccines. For routine childhood vaccines given to healthy children, confounding by indication is not a significant concern. Because currently licensed vaccines are preventive rather than therapeutic, the protopathic bias does not need to be accounted for; in fact, acute symptoms are more likely to result in deferral of vaccination.[25] Whereas polypharmacy, particularly in older adults, has been associated with a variety of drug interactions and adverse outcomes, co-administration of indicated vaccines is a standard of care practice for both adult and childhood immunisation.[26]

For comprehensive assessment of vaccine safety, what is needed is capture of clinical events under

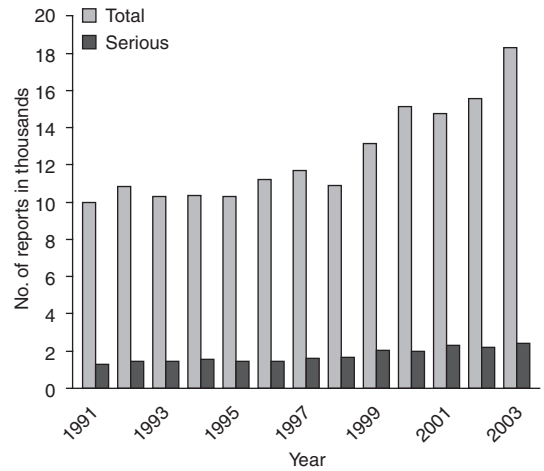

Fig. 2. Number of reports (in thousands) to the US Vaccine Adverse Event Reporting System, 1991–2003.[18]

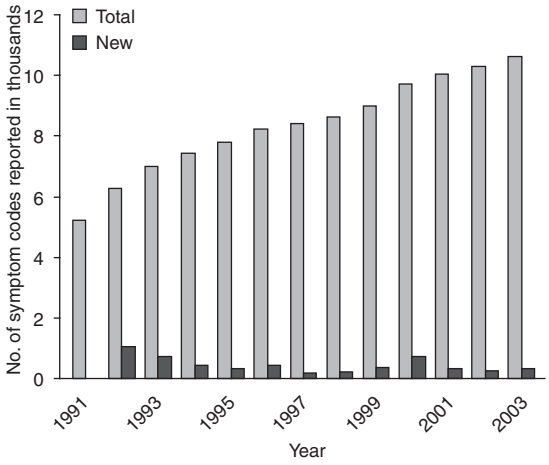

Fig. 3. Number of separate symptom codes reported to the US Vaccine Adverse Event Reporting System, 1991–2003.[18]

study in both vaccinated and unvaccinated individuals. In the US, programme infrastructure exists to support childhood vaccination (e.g. through the Vaccines for Children programme) and nationally representative vaccine coverage surveys are conducted annually. However, under the current US healthcare and public health infrastructure, there is no national repository of vaccination activity from which the total numbers of persons receiving a vaccine or specific combination of vaccines can be obtained. VAERS, which operates separately from the vaccine programme, provides only partial information on a subset of cases involving vaccinees who have experienced and reported adverse events.[27]

Traditional epidemiological approaches to vaccine-safety databases include calculation and comparison of crude reporting rates based on manufacturer supplied dose distribution data; however, such approaches are best suited to vaccines sharing similar target diseases, ages and schedules.[28,29] Because spontaneous reporting systems such as VAERS are limited by their lack of denominator data, the idea of surrogate denominators internal to the system, borrowed from proportionate morbidity ratio methodology, was developed.[23,30]

Figure 4 illustrates calculation of the proportional reporting ratio (PRR) within VAERS, which compares proportions of events for a given vaccine with proportions for another vaccine or for a group of vaccines. An event with a higher proportion for the study vaccine than for other vaccines might be considered a signal and require further study.[31] A PRR of 2 is generally considered a minimal threshold for further review, though the absolute number of case reports involved for the vaccine of interest must also be taken into consideration.[24] PRR can also be monitored for time trends of increase, decrease or persistent elevation.[32] Related methods including Bayesian and neural network approaches[33-35] calculate similar measures of disproportionality of vaccine-adverse event pairs but adjust them for specific features of the data.

Association rule discovery (ARD), or so called 'market basket' analysis, has also been applied to VAERS data for detection of multisymptom syndromes, symptom interactions, and inter-vaccine interactions that are seen proportionally more frequently following specific vaccines.[36] This technique, which has been widely used in market research and genetics,[37,38] appears to be suitable for some analyses within VAERS. It can be conceived of as multisymptom PRR.

Similar methods used in drug safety research have included the reporting odds ratio (ROR)[39] and the FDA Multi-Item Gamma Poisson Shrinker (MGPS) programme.[40] ROR accounts for syndromes and potential interactions by use of covariates and interaction terms. MGPS computes signal scores for three item and higher combinations of drugs and events that are significantly more frequent than predicted.

Although both PRR and ARD involve screening for events over-represented among specific vaccine

	Reported VAE "Y"	Other reported VAE
Reports following vaccine "X"	a	b
Reports following other vaccines	c	d

$$PRR = \frac{a / (a + b)}{c / (c + d)}$$

Fig. 4. Calculation of the proportional reporting ratio (PRR) in the US Vaccine Adverse Event Reporting System. A potential signal may warrant further investigation for a PRR >2, where 'a' is >3. **VAE** = vaccine adverse event.

reports compared with reports following other vaccines, so-called 'historic limits' methods screen for unusual increases in the monthly number of reports having specific vaccine-event combinations. In their simplest form, historic limits involve instances such as the first report of a novel symptom code. More generally, they can be conceived of as comparisons of 'past period' averages with current period report counts.

From a public health perspective, historic limits methods including time-series and scan statistics serve to detect aberrations from the 'baseline' occurrence of health events under surveillance.[41] Newer applications of this family of methods include syndromic surveillance algorithms designed to detect disease outbreaks potentially related to bioterrorism.[42]

Additional specialised advanced signal detection techniques are also being developed for use within VAERS. Automated screening for nonrandom clustering of event-specific symptom onset intervals following vaccination[43] has been successfully pilot tested. So called 'positive rechallenges', in which symptoms recur after a subsequent vaccine in a series, have been flagged within VAERS for additional review since 1995.[44]

5. Objectives of Advanced Signal Detection

Regardless of the methodology employed, all data-mining techniques are designed to serve one or more of the following purposes:

- Identification of unknown (previously undetected) signals, consistent with the WHO definition of what constitutes a signal[45] or 'potential signal', and with the hypothesis generating function of VAERS.[3]
- Provision of supplemental evidence (either favouring or refuting the proposed adverse event) for safety concerns identified by traditional 'case finding' means.
- Ascertainment of possible syndromes of related symptoms or groups of symptoms associated with a particular vaccine or vaccines.
- Similarly, identifying or investigating potential vaccine-vaccine interactions, which may involve issues of vaccine safety and/or efficacy.[46] In general, vaccine efficacy and/or immunogenicity are better studied in prelicensure or phase IV postmarketing studies, due to availability of more complete data.

These objectives must be considered in context of the primary role of VAERS in vaccine vigilance, that of detecting signals and generating hypotheses; data-mining methods are not currently used by CDC or FDA researchers as signal evaluation or confirmation methods.[30]

6. Specific Examples from VAERS Experience

6.1 Identification of Unknown (Previously Undetected) Signals

A joint FDA-CDC assessment of the postlicensure safety profile of newly licensed oral and injectable typhoid vaccines employed PRR methodology to identify minor but previously undocumented adverse events including dizziness, pruritus, fatigue and myalgia.[47] Disproportionality assessment is also now routinely conducted as part of safety surveillance for vaccines with newly expanded recommendations, such as inactivated influenza vaccine (IIV) in 6–23 month olds.[48]

6.2 Provision of Supplemental Evidence

The most notable case of the use of a simple type of historic limits approach within VAERS involves the fact that when intussusception following rotavirus vaccine came to attention in 1999, it was noted that no reports of this condition had been received previously following the administration of any vaccine.[28] Following this line of reasoning, each newly reported symptom represents a potential 'striking case' that may warrant further investigation, although many such reports involve coincidental occurrences post-vaccination. Historic limits methodology was also used to identify administration errors involving tetanus toxoid-containing vaccines and tuberculosis skin tests in 2004.[49] Clusters or single cases of inadvertent substitution errors of these two products were identified in multiple states. This instance, which involves a previously identified programmatic error,[50] highlights the role of

data mining in drawing attention to adverse events that are geographically or temporally clustered.

A signal of Bell's palsy following IIV, which was primarily identified by case review and case series analysis, was supported by an elevated PRR of nearly 4.[51] This signal appears to have been confirmed, albeit weakly, in a large linked-database study in the US.[52]

6.3 Ascertainment of Possible Syndromes

PRR analysis also provided retrospective evidence that IIV associated oculo-respiratory syndrome (ORS) cases had been reported to VAERS prior to the identification of ORS in Canada.[32] ORS, which is clinically difficult to distinguish from allergic rhinoconjunctivitis, also appears to be identifiable within the VAERS database using associational analysis. Various combinations of ocular and upper respiratory-related findings appear among the top 'association rules' for IIV.[53]

Additionally, researchers have undertaken data-mining studies in VAERS that are primarily methodological in nature, seeking to assess whether accepted signals can be detected and to compare features of different methods. In 2001, Niu et al.[54] from the FDA reported that intussusception and possibly related gastrointestinal symptoms were successfully identified by use of a Bayesian data-mining method closely related to PRR. Application of ARD in a retrospective analysis yielded known associations involving MMR, DTaP and rotavirus vaccines.[36] The use of multiple methods simultaneously may increase the sensitivity of data mining, but can also flag large numbers of apparent false-positive signals.[55] 'Side-by-side' comparisons of related data-mining approaches may allow public agencies with limited information technology resources to prioritise expenditures for data-mining software.[39,56]

7. Limitations and Criticisms of Advanced Signal Detection Methods

Since all data-mining methods are essentially specialised types of proportional morbidity analyses, they share many common limitations.[57] Such measures cannot be used to calculate incidence or estimate risks or relative risks of VAEs. PRR and related methods discussed in this paper should be clearly understood as nonpopulation-based measures. Just as the proportion of cancers of a given organ relative to all cancers may reflect underlying population factors unrelated to differential risk of cancers, so different distributions of VAEs between vaccines may reflect differences in characteristics of vaccinated populations or individuals involved in adverse event reports.[3]

All 'disproportions' must be subject to case series level review for clinical coherence and alternative explanations should always be sought and considered.[30] Reviewers should pay particular attention to possible coding errors or reports of unconfirmed conditions. Within passive surveillance systems, disproportionality may reflect biases related to either vaccine usage or adverse event reporting.[58] It cannot be stressed heavily enough that elevations in PRR or other data-mining statistics do not necessarily reflect a causal relationship between a vaccine-adverse event pair. Similarly, references to 'relative risks' or 'risk ratios' based on data internal to VAERS should be viewed circumspectly, keeping in mind the nonpopulation-based nature of the system.[3] Inappropriate inference of causality is an inherent problem of spontaneous reporting systems, not one specific to data-mining methods.[59]

Regardless of the signal generation methods used within VAERS, with few exceptions,[8] testing of such signals in cohort or other epidemiologic studies is needed for confirmation of theorised vaccine adverse event associations. Initial concerns identified in VAERS may be verified[60] or found to have been false signals due to reporting biases.[61] Perhaps surprisingly, most signals identified from VAERS have been confirmed on follow-up study. In the case of intussusceptions, the initial VAERS case series correctly identified not only the clinical event, but also the time and dose specific risk window.[62] Even when signals are detected and validated, changes in immunisation policy may not be warranted.[63] Evaluation and prioritisation of signals for controlled study represents an important emerging field; available tools include guidances for good pharmacovigilance practices,[64] standardised case definitions[65] and expert reviews by oversight panels.[66]

Although the overall quality of passively reported data[67] remains a concern, this criticism must be

considered in the context of VAERS stated purpose of hypothesis generation, not signal evaluation. Web-based reporting has been shown to have a positive impact on VAERS data quality and completeness.[68] Additional methods of improving reported data, including linkages with registries and other immunisation information systems, are being pursued. Prelicensure trials and postlicensure epidemiologic studies are resource and labour intensive, and cannot actively seek all potential adverse outcomes related to vaccination.[69] The recent discovery of the rare association of the New York City Board of Health (NYCBOH) strain of smallpox vaccine with myo/pericarditis, despite extremely widespread prior use of the vaccine, should serve as a cautionary tale regarding the limits of our safety knowledge about vaccines.[70]

One persistent concern regarding data-mining approaches to vaccine and drug safety is that these methods will be used to the exclusion of clinical reasoning and judgment.[71] A closely related critique is that signal prioritisation will be based solely on ranking of data-mining statistics.[59] Advanced signal detection methods are best viewed not as stand alone signal detection methods, but as valuable additions to the pharmacoepidemiologic 'toolbox' in an era of technological acceleration, novel reporting channels and vast numbers of spontaneous reports that are beyond the capacity of either public or private organisations to perform systematic case level review.[72] Properly implemented and conservatively interpreted statistical results are another arrow in the quiver of the trained vaccine-safety reviewer. Drug safety experts have reached similar conclusions.[73,74]

Specific categories of outcomes that may pose special difficulties for study by a data-mining approach include pregnancy outcomes, suspected vaccine failures and neurodevelopmental disabilities. Reasons include potential reporting biases,[2] coding issues[3] and lack of systematic validation of outcomes of interest; however, these issues apply to spontaneous reporting systems in general, not only to quantitative signal detection approaches.[75] Registries are more appropriate study settings for pregnancy exposures[76] and suspect vaccine failures.[77] Concerns about neurodevelopmental disabilities in relation to vaccination are better studied in longitudinal cohort[78] and case control[79] studies and have also been the subject of multiple systematic reviews.[80,81]

8. Future Directions for Data Mining in VAERS

The primary use for data mining within VAERS so far has been signal clarification for adverse events identified by traditional means, but *de novo* signal generation via data mining is beginning to occur and may represent the future of these techniques. While keeping in mind the limitations of advanced signal detection approaches, in the interest of efficiency researchers in VAERS are working towards periodic automated screening of the VAERS database using a 'toolbox' of PRR, ARD, and historic limits methods. In order to make the best use of information available within VAERS, variables being used or explored in automated screening methods include vaccine type or combination, dose and lot number, event type, seriousness, age, sex and geographic location.

Any disproportionate representation of VAE characteristics in a subset of reports, represent potential signals that must be further scrutinised both clinically and epidemiologically. Data mining increases rather than decreases the importance of the clinical reviewer in evaluating postlicensure vaccine-safety concerns. Prioritisation of signals for further study will therefore become more important and some formal guidance in this field is emerging.[64]

The increasing complexity of the immunisation-delivery and vaccine-safety environments has made the development of multiple approaches necessary, including automated signal detection in VAERS, which are more proactive and less reactive in assessing vaccine-safety concerns.[21,82] The Vaccine Safety Datalink (VSD) has also successfully tested 'rapid cycle' analysis, which may flag-safety signals requiring further study very soon after vaccine introduction.[83] VSD rapid cycle analysis may be used to complement VAERS in detecting potential problems related to newly licensed or recommended vaccines.

9. Conclusions

Data presented in this paper indicate the increasing complexity of the VAERS database, seen for both vaccine exposures and reported adverse events or symptoms. The most important consequence of a larger and more complicated dataset is the increasing challenge of the early detection of potential vaccine-safety problems. Traditional case-finding methods should be supplemented by advanced signal detection to assure timeliness. Many data-mining methods, such as onset interval clustering detection and simple historic limits methods represent logical extensions of traditional signal detection methods.[43,49,51] Although data mining has inherent limitations, if it is correctly used and understood it represents another tool to increase the sensitivity of the VAERS in detecting potentially vaccine-related adverse events.

Historically, vaccine-safety science has evolved in a public health environment in which new vaccines are introduced singly.[84,85] VAERS was used to generate hypotheses about whether adverse event y had been reported after vaccine x, leading to research studies in the VSD[86] or other settings of whether event y was causally associated with vaccine x.

Several recently licensed or soon-to-be licensed products, including MCV, Tdap and human papillomavirus vaccines, will have overlapping recommended age or risk groups. Questions regarding safety of co-administration and acceptable inter-vaccine intervals will naturally be raised. Vaccine-safety surveillance systems will also need to be able to provide data about the safety of potentially unavoidable administrations of extra doses of vaccine[26] as well as identify potential interactions between vaccines related to either efficacy or safety.

In pharmacovigilance, signals from all possible sources should be sought in the interest of safeguarding public health. Data mining is only one of several improvements to the vaccine-safety infrastructure of VAERS implemented or in progress in recent years.[21] Enhanced surveillance through VAERS and the potential use of VSD rapid cycle analysis will be needed to ensure rapid detection of any emerging safety concerns.

Acknowledgements

The authors would like to thank Robert T. Chen, John Sawyer, Penina Haber, Alena Khromova, Frank Destefano, Lauren Dimiceli, Thomas Verstraeten.

Funding Source: US Government. The authors have no conflicts of interest that are directly relevant to the content of this manuscript.

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