

# Advanced Clinical Decision Support for Vaccine Adverse Event Detection and Reporting

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**Background.** Reporting of adverse events (AEs) following vaccination can help identify rare or unexpected complications of immunizations and aid in characterizing potential vaccine safety signals. We developed an open-source, generalizable clinical decision support system called Electronic Support for Public Health–Vaccine Adverse Event Reporting System (ESP-VAERS) to assist clinicians with AE detection and reporting.

**Methods.** ESP-VAERS monitors patients' electronic health records for new diagnoses, changes in laboratory values, and new allergies following vaccinations. When suggestive events are found, ESP-VAERS sends the patient's clinician a secure electronic message with an invitation to affirm or refute the message, add comments, and submit an automated, prepopulated electronic report to VAERS. High-probability AEs are reported automatically if the clinician does not respond. We implemented ESP-VAERS in December 2012 throughout the MetroHealth System, an integrated healthcare system in Ohio. We queried the VAERS database to determine MetroHealth's baseline reporting rates from January 2009 to March 2012 and then assessed changes in reporting rates with ESP-VAERS.

**Results.** In the 8 months following implementation, 91 622 vaccinations were given. ESP-VAERS sent 1385 messages to responsible clinicians describing potential AEs. Clinicians opened 1304 (94.2%) messages, responded to 209 (15.1%), and confirmed 16 for transmission to VAERS. An additional 16 high-probability AEs were sent automatically. Reported events included seizure, pleural effusion, and lymphocytopenia. The odds of a VAERS report submission during the implementation period were 30.2 (95% confidence interval, 9.52–95.5) times greater than the odds during the comparable preimplementation period.

**Conclusions.** An open-source, electronic health record–based clinical decision support system can increase AE detection and reporting rates in VAERS.

**Keywords.** vaccine; immunization; adverse reaction; reporting; adverse event.

Routine vaccination is a cornerstone of preventive healthcare. Vaccines have dramatically decreased the incidence of many serious infectious diseases [1]. While precensure clinical trials help to characterize the basic safety profiles of vaccines, rare adverse events

(AEs) may only become apparent after widespread use in the community. To this end, rigorous postmarketing vaccine safety surveillance is critical to building public and professional trust in vaccines.

The Centers for Disease Control and Prevention (CDC) and the US Food and Drug Administration (FDA) jointly operate the Vaccine Adverse Event Reporting System (VAERS). VAERS is a national passive reporting system that accepts spontaneous AE reports from clinicians, pharmaceutical companies, and the public. Strengths of VAERS include its national scope and its ability to elicit timely and potentially detailed clinical information that may be relevant to understanding the event and developing hypotheses about conditions that predispose to the

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event. VAERS also has the ability to detect rare AEs. These rare events, which may raise potential safety concerns, can be further studied in carefully designed, rigorous epidemiological studies in other systems in place to complement VAERS reporting, including the Vaccine Safety Datalink and Mini-Sentinel [2, 3].

VAERS reports vary in quality and completeness, and underreporting, especially of mild and self-limiting AEs, appears to be common [4, 5]. Reasons for clinician underreporting might include failure to associate an acute health event to recent vaccines, lack of awareness of VAERS, the misperception that only serious events should be reported, and lack of time to report. VAERS reports often lack critical data such as vaccine lot numbers and the precise date of vaccination [6]. Currently no widespread, automated mechanisms exist to facilitate detection and electronic reporting of AEs to VAERS by clinicians. Consequently, the utility of VAERS data is diminished by substantial underreporting and sparse documentation of patients' clinical status and potential explanations of their conditions [4, 7].

One potential adjunct is to take advantage of the increasing penetration and functionality of electronic health records (EHRs). Adding surveillance and AE reporting capacity to EHRs offers a practical and efficient means to monitor large numbers of patients, integrate AE reporting into physicians' workflow, elicit clinician comments in a timely manner, and efficiently submit reports. We describe the development and implementation of an EHR-based AE detection and reporting system called Electronic Support for Public Health–Vaccine Adverse Event Reporting System (ESP-VAERS) that builds upon an automated vaccine AE surveillance system based in an ambulatory electronic medical record [6]. ESP-VAERS identifies possible AEs following vaccination, prompts clinicians for input when appropriate, and has the capability to submit secure electronic reports to VAERS. The ESP-VAERS design is open-source and compatible with any modern EHR.

## PATIENTS AND METHODS

### Study Setting

ESP-VAERS was implemented in the MetroHealth System, a tertiary care academic health system in northeast Ohio that provides a full range of inpatient and outpatient primary and specialty care services and has a network of community health centers that primarily focus on primary care and preventive health services. The MetroHealth system includes >500 primary care and specialty care physicians and 373 000 established patients with nearly 1 million medical encounters per year. Both the academic medical center and the community provider network are served by an integrated EpicCare EHR [8]. All adult and pediatric patients served by MetroHealth were included in the study.

MetroHealth utilizes the Electronic Support for Public Health network (ESPnet) public health surveillance platform

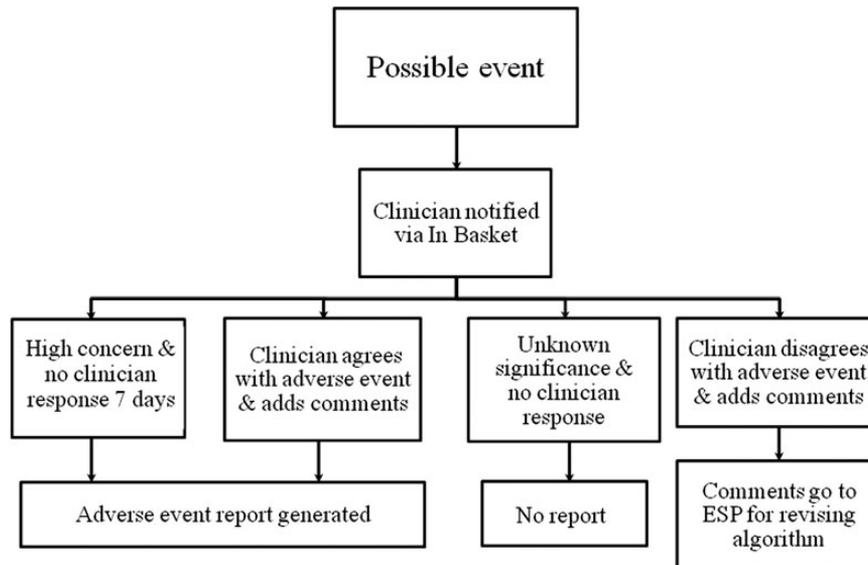
[9]. ESPnet is open-source software that facilitates automated detection and reporting from EHRs to health departments [10, 11]. ESPnet is populated nightly with structured data from the EHRs on all patients seen throughout the healthcare system within the preceding 24 hours. These data include demographics, diagnoses, laboratory reports, prescriptions, and vaccines. ESPnet organizes these data into tables, applies algorithms to detect events of public health interest, and, when appropriate, sends electronic case reports to the state health department. MetroHealth has been using ESPnet for automated notifiable disease surveillance and electronic reporting to the Ohio Department of Health since 2009 [12].

### Development of ESP-VAERS

We developed a new ESPnet module, ESP-VAERS, to monitor patients' EHRs for 42 days following each vaccination for possible new onset AEs. ESP-VAERS identifies every vaccine administered and prospectively records the patient's new diagnostic codes, laboratory tests, allergy lists, and medication prescriptions during the 6-week surveillance period. We developed and applied algorithms designed to detect both expected and unexpected AEs. When a possible AE is identified based on the algorithms, it is recorded in a registry database table and the clinician is automatically sent a secure electronic message through the EHR to consider if the event should be reported to VAERS (Figure 1).

### Algorithm Development

We divided *International Classification on Diseases, Ninth Revision (ICD-9)* diagnosis codes into 3 categories: (1) codes for severe and/or potential high-probability diagnoses that have been previously associated with vaccines [13, 14]; (2) codes for diagnoses of undetermined significance that could conceivably be associated with vaccines; and (3) codes for diagnoses that are not associated with receipt of vaccines (eg, well child visits, fractures) (Supplementary Material). Category 1 included ICD-9 codes for severe and potential high-probability diagnoses included in the VAERS Table of Reportable Events Following Vaccination [13] and the Vaccine Injury Table [14] and ICD-9 codes defined as immunization reactions. The onset intervals and exclusion criteria for each diagnosis were based on the VAERS Table of Reportable Events Following Vaccination [13]. Category 2 included all ICD-9 codes other than the potential high probability and severe event codes in category 1, the extremely low probability codes in category 3, and any codes present in the individual patient's record within the preceding 36 months. Onset intervals and additional exclusion criteria for these codes were based on clinical expertise, literature review, and review of alerts using retrospective and pilot project data. Codes for routine care and diagnoses very unlikely to represent AEs following vaccination were placed into category 3 and did not trigger an alert.



**Figure 1.** Flowchart of possible vaccine-related adverse events. Abbreviation: ESP, Electronic Support for Public Health.

We assessed for significant changes in key laboratory tests following vaccination including hemoglobin, white blood cell count, platelet count, creatinine, alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, bilirubin, sodium, potassium, calcium, creatinine kinase, and partial thromboplastin time. We set different thresholds for significant changes for each laboratory test ([Supplementary Material](#)). In general, a significant change was defined as substantial worsening compared to the patient's most recent test result or an abnormal result without a prior record of any results since ESPnet's inception on 1 January 2009. ESPnet also followed the patient's coded allergy list for 30 days after vaccination. The appearance of a new allergy to the index vaccine was considered suggestive of an adverse event.

Possible and probable AE messages were sent to clinicians' Epic In Basket, a secured system for clinicians to communicate with one another regarding patient care within the EHR [8]. Each message contained a brief summary including patient name, vaccination, suspected AE, dates of vaccination and diagnosis of the suspected AE, and a hyperlink to a Web form with more information. Selecting the hyperlink opened a Web form with details about the vaccination, adverse event, and options to approve and send the notification to VAERS with optional comments or cancel the notification and add optional comments. The hyperlink also included 3 questions about the utility and acceptability of the message:

1. Was this message helpful? (Yes/No)
2. Did it interrupt your workflow? (Yes/No)
3. Has the number of messages recently been Appropriate or Too Frequent?

Reports of severe and potential high probability AEs following vaccination, such as anaphylaxis and encephalitis, were submitted automatically even if the clinician did not respond to the message. Reports sent to VAERS included the patient's demographics, vaccine, lot number, date of vaccination, possible AE, date of AE, and any free-text comments provided by clinicians. If multiple vaccines were given simultaneously, information on all vaccines were included in the report as per the standard VAERS protocol [15]. Cases approved for transmission were sent to VAERS as HL7 version 2.3.1 messages using the CDC's PHIN-MS secure messaging protocol [16].

Following implementation and testing by co-investigators and clinician collaborators, MetroHealth clinicians were offered brief training sessions at staff meetings to ensure that they were familiar with the project and comfortable managing the notifications. Support for clinicians using the ESP-VAERS system was provided through handouts, teaching sessions, and an EHR message to all clinicians. The ESP-VAERS study period ran from 4 December 2012, the date that the system was implemented in all MetroHealth practices, to 3 August 2013.

### Historical Reports

We queried the VAERS database for all reports sent from the state of Ohio from 1 January 2009 to 31 March 2012, limiting the search to reports sent from 4 December to 3 August in each year to match the study period. Based on city, name of the clinic or hospital, address of the clinic or hospital, and/or provider name, we identified reports sent from the MetroHealth System and verified these reports in the EHR. The number of vaccinations in the historical period was determined by running ESP-VAERS on all MetroHealth data from 1 January 2009 to 3

**Table 1. Vaccines Administered Throughout the MetroHealth System, 4 December 2012 to 3 August 2013 (N = 91 622)**

Vaccine	Count, No. (%)
Tdap	15 279 (16.7)
IIV	13 629 (14.9)
PCV13	7561 (8.3)
Hib	7051 (7.7)
Hepatitis A pediatric	6508 (7.1)
HPV	5424 (5.9)
DTaP-hepatitis B-IPV	5099 (5.6)
PPSV23	4230 (4.6)
Pentavalent rotavirus	3087 (3.4)
Other vaccines	23 754 (25.9)

Some adverse events were counted against multiple vaccines if the patient received >1 vaccine at the index encounter.

Abbreviations: DTaP, diphtheria, tetanus, and pertussis; Hib, *Haemophilus influenzae* type B; HPV, human papillomavirus; IIV, inactivated influenza vaccine; IPV, inactivated polio vaccine; PCV, pneumococcal conjugate vaccine; PPSV23, 23-valent pneumococcal polysaccharide vaccine; Tdap, combined tetanus, diphtheria, and pertussis.

August 2009; 4 December 2009 to 3 August 2010; 4 December 2010 to 3 August 2011; and 4 December 2011 to 31 March 2012.

### Statistical Analysis

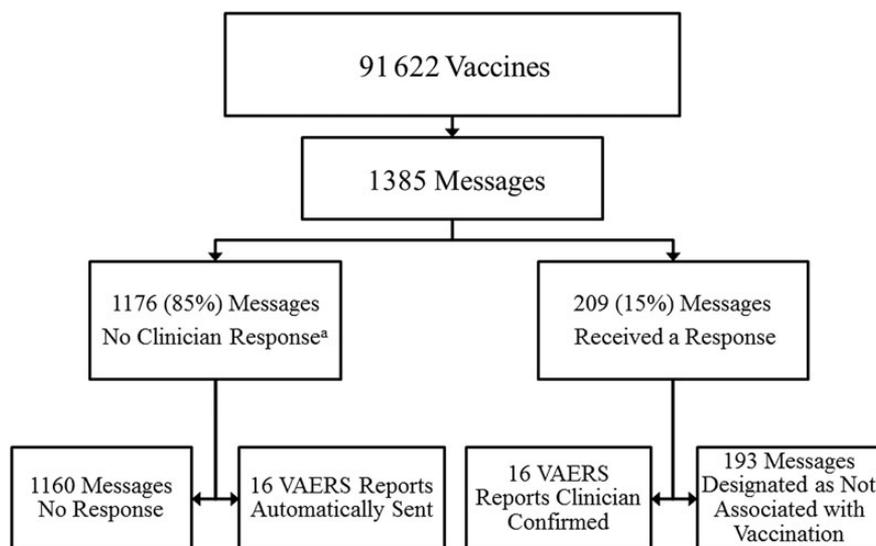
Using logistic regression, we compared the odds of a VAERS report after vaccination in the implementation period to the odds of a report in the historical period. We controlled for the time of year by restricting the historical reports to the period of calendar time relevant to the postimplementation period.

The study was approved by the institutional review boards of the MetroHealth System and Harvard Pilgrim Health Care Institute. We employed best-practice methods to ensure Web application security, strong message encryption, and other techniques to ensure that these data were protected at or beyond standards set by the American National Standards Institute Healthcare Information Technology Standards Panel [17].

### RESULTS

During the 8-month study period, 91 622 vaccinations were administered. The most common vaccines given were the combined tetanus, diphtheria, and pertussis vaccine (Tdap) (15 279 doses) and the inactivated influenza vaccine (13 629 doses) (Table 1). ESP-VAERS sent 1385 messages to responsible clinicians describing possible AEs following vaccination, corresponding to a rate of 15 messages per 1000 vaccinations (Figure 2). The average number of alerts per clinician was 0.4 messages per month, and the range was between 0 and 8 messages per month.

Clinicians opened 1304 messages (94.2%), responded to 209 messages (15.1%), and confirmed 16 for transmission of reports to VAERS (Table 2). The diagnoses for transmitted reports included seizure, eosinophilia, Bell's palsy, pleural effusion, lymphocytopenia, leukopenia, cellulitis, febrile seizure, rash, viral exanthem, rubella symptoms, fever and mild neutropenia, fever, and hypothyroidism. Of the 16 confirmed messages, 15 included custom comments from the healthcare provider, and 9 of the 16 reports were sent on pediatric patients. The remaining 193 alerts were designated by clinicians as not associated with the vaccination. The most common diagnoses, designated



**Figure 2.** Flowchart of vaccine-related data from the MetroHealth System, 4 December 2012 to 3 August 2013. <sup>a</sup>94% of all messages were opened. Abbreviation: VAERS, Vaccine Adverse Event Reporting System.

**Table 2. Vaccine Adverse Event Reporting System Reports Sent From the MetroHealth System, 4 December 2012 to 3 August 2013**

Adverse Event	Vaccine(s) Administered
<b>Clinician confirmed (n = 16)</b>	
Seizure	IIV
Eosinophilia	IIV
Eosinophilia	PCV13
Bell's palsy	Tdap
Pleural effusion	IIV, Tdap
Lymphocytopenia	Tdap
Leukopenia	Tdap
Cellulitis	DTaP-IPV, MMRV
Febrile seizures, rash	MMR, varicella
Viral exanthem, rubella symptoms	DTaP, hepatitis B, IPV, Hib, IIV, MMR, varicella, PCV13
Fever and mild neutropenia	PPSV23
Rash	DTaP-IPV, MMRV
Rash	Hepatitis A, Hib, MMR, PCV13, varicella
Rash	Hepatitis A, MMRV
Fever	DTaP-hepatitis B-IPV, Hib, PCV13, rotavirus
Hypothyroidism	Shingles, Tdap
<b>Automatically sent (n = 16)</b>	
<b>ICD-9 codes for immunization reaction</b>	
Reaction to vaccine—possible allergic reaction	IIV
Fever, local immunization reaction	DTaP-IPV, MMRV
Rash, fever	Hepatitis A, MMR, varicella
Rash, fever	Hepatitis A, MMR, varicella
Fever	DTaP-hepatitis B-IPV, Hib, PCV13, rotavirus
Cellulitis	IIV, meningococcal
Fussiness	Hepatitis A, MMRV
Local immunization reaction	DTaP-IPV, MMRV
Local immunization reaction	DTaP-IPV, hepatitis A, MMRV
Local immunization reaction	Hepatitis A, MMR, varicella
Local immunization reaction	HPV, meningococcal, Tdap
Local immunization reaction	IIV
Local immunization reaction	IIV, PPSV23, Tdap
Local immunization reaction	PPSV23
Local immunization reaction	Shingles
Local immunization reaction	Tdap

Abbreviations: DTaP, diphtheria, tetanus, and pertussis; Hib, *Haemophilus influenzae* type B; HPV, human papillomavirus; ICD-9, International Classification on Diseases, Ninth Revision; IIV, inactivated influenza vaccine; IPV, inactivated polio vaccine; MMR, measles, mumps, and rubella; MMRV, measles, mumps, rubella, and varicella; PCV, pneumococcal conjugate vaccine; PPSV23, 23-valent pneumococcal polysaccharide vaccine; Tdap, combined tetanus, diphtheria, and pertussis.

as not associated with the vaccination, included bronchospasm, nonspecific skin eruption, cellulitis, fever, and seizure. These 5 diagnostic categories accounted for 25.9% of all of the alerts that were considered not associated with the vaccination.

An additional 16 high-probability AEs following vaccination were sent automatically as the clinician did not respond to the alert (Table 2). All of the high-probability reports were coded by clinicians as immunization reactions. These included possible allergic reaction, fever alone, fever and a local reaction, fever and rash, cellulitis, and fussiness, and 9 of these 16 reports were based on diagnoses in pediatric patients. Thus, 32 VAERS reports were sent for 91 622 vaccines over an 8-month period for a net reporting rate of 34.9 VAERS reports per 100 000 vaccinations (Table 3).

Of the 1160 alerts without a response and not automatically sent, the most common diagnoses (accounting for 19.2%) included nonspecific skin eruptions, eosinophilia, seizure, fever, leukopenia, and lymphocytopenia.

We identified 3 reports in VAERS that were sent by MetroHealth clinicians from 1 January 2009 to 3 August 2009; 4 December 2009 to 3 August 2010; 4 December 2010 to 3 August 2011; and 4 December 2011 to 31 March 2012, prior to the inception of ESP-VAERS. During this period, 274 080 vaccines were administered at MetroHealth, corresponding to a reporting rate prior to the implementation of ESP-VAERS of 1.09 reports per 100 000 vaccinations. The odds of a VAERS report submission during the study period were 30.2 (95% confidence interval, 9.52–95.5) times greater than the odds during the comparable preintervention period.

Many clinicians felt that the messages were helpful (115/209 [55.0%]) and did not interrupt workflow (116/209 [55.5%]). The majority of the clinicians (166/209 [79.4%]) stated that the number of messages was appropriate.

## DISCUSSION

Our implementation of ESP-VAERS demonstrates that EHRs can facilitate identification of possible AEs following vaccination, engage clinicians within their existing workflows to comment on events, and generate and submit secure reports to VAERS. Implementation of ESP-VAERS was associated with a 30.2-fold increase in the odds of MetroHealth submission of AE reports to VAERS. Many reported AEs were medically significant, including seizure, lymphocytopenia, and Bell's palsy, and other AEs such as pleural effusions have only rarely been reported following vaccination [18]. Such reporting might provide hypothesis-generating information to the CDC and FDA that results in further assessment of a possible association. We demonstrated that an open-source, EHR-based clinical decision support system improves the detection and reporting of AEs following vaccination.

Through this study, we developed new logic for automated identification of potential high probability and possible AEs following vaccination, developed capacity for querying clinicians via the EHR from an external source, and implemented automated secure HL7 messaging to VAERS. Such a system is dependent upon clinician acceptance and participation. Many of

**Table 3. Vaccine Adverse Event Reporting System Reports Sent From the MetroHealth System During the Study Period Versus Before the Study Period**

MetroHealth Data	No. of VAERS Reports	Time Period	No. of Reports per Month	No. of Vaccinations	No. of Reports per 100 000 Vaccinations
Preimplementation data	3	27 mo	0.11	274 080	1.09
Implementation data	32	8 mo	4	91 622	34.9

Abbreviation: VAERS, Vaccine Adverse Event Reporting System.

the clinicians found that the messages were helpful and did not interrupt their workflow. Most found that the number of messages sent was appropriate.

EHRs offer an increasingly available opportunity for low-cost monitoring and reporting of AEs. EHRs offer 3 potential advantages over existing claims-based systems: (1) EHRs have access to much richer data streams, including vital signs and laboratory test results; (2) EHR data streams are updated in near-real-time, permitting more timely AE detection compared with claims databases; and (3) EHR systems can query patients' clinical providers for comments on possible AEs in near-real time, adding richness and specificity to AE detection.

ESP-VAERS provides potential advantages over traditional passive reporting systems: ESP-VAERS prompts clinicians to recognize possible AEs and automates components of the VAERS reporting process. Thus, the increased rate of VAERS report submission during the intervention period might be due to a combination of alerting clinicians to possible AEs that they may have otherwise missed or disregarded, notifying clinicians to consider reporting the AE to VAERS, and facilitating the report submission process. In addition, because they contain rich data on large numbers of patients, automated EHR surveillance systems can facilitate estimation of possible AE incidence densities in defined populations. In contrast, data from passive surveillance yield AE counts only for those reports submitted. Finally, ESP-VAERS reports can be prepopulated with information from the EHR, allowing for additional comments from a clinician, thus limiting the likelihood of reports with missing key data fields. This is in contrast to traditional passive VAERS reports, which have been found to be missing essential variables including age, date of birth, vaccination date, and date of AE onset [19]. As ESP-VAERS is not embedded within an EHR, but rather sits outside of the EHR, it does not burden routine EHR operations. Use of EHRs is increasingly common, so a generalizable and portable automated AE surveillance approach based on existing EHRs potentially offers a feasible solution to quickly ramp up AE surveillance to provide clinically rich reports at relatively low marginal cost.

Limitations to ESP-VAERS include the large number of alerts and the interrelated risk of clinician alert fatigue. Although clinicians opened 94.2% of the AE reports we sent, they only elected to respond to 15.1%. Further investigation into the large number

of opened alerts that lack a response is warranted. The current algorithm is restricted to single codes for new diagnoses and historical events. Increasing the sophistication of the algorithm and program to use combinations of *ICD-9* codes and laboratory values for diagnoses and exclusion criteria may reduce the number of false-positive alerts that clinicians are receiving. Furthermore, transitioning to *ICD-10* may decrease the false-positive alerts given the greater richness of *ICD-10* codes for specific diagnoses compared with *ICD-9* codes [20].

## CONCLUSIONS

An open-source, EHR-agnostic clinical decision support system with advanced predictive algorithms using *ICD-9* codes, laboratory values, allergies, and the potential for medication prescriptions can significantly improve the detection and reporting of AEs following vaccination to VAERS. This type of open-source, advanced clinical decision support system can provide new opportunities for clinical decision support to improve public health.

## Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online (<http://cid.oxfordjournals.org>). Supplementary materials consist of data provided by the author that are published to benefit the reader. The posted materials are not copyedited. The contents of all supplementary data are the sole responsibility of the authors. Questions or messages regarding errors should be addressed to the author.

## Notes

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**Potential conflicts of interest.** All authors: No potential conflicts of interest.

All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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