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# Use of an Electronic Monitoring System for Self-Reporting Smallpox Vaccine Reactions

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*Objectives:* **Tracking vaccine reactions and adverse events during a large-scale vaccination program such as the recent smallpox program or a pandemic flu outbreak will be a challenge. We report on vaccine reaction data collected using a novel telephone- and web-based electronic reporting system. The system was used to monitor vaccinees during the U.S. Army's smallpox vaccination campaign, which was part of the national program to prepare against biological attack. In addition, we report on the time course of events after smallpox vaccination based on the self-reported data and evaluate the validity and reliability of self-reported take information after smallpox vaccination.**

*Methods:* **A prospective cohort of subjects receiving the smallpox vaccination volunteered to use an electronic monitoring system to track and report their vaccination reactions.**

*Results:* **Users made 6.8 ± 6.2 (mean ± SD) reports using the electronic monitoring system. The sensitivity and positive predictive value of self-reported takes were high, 98.8% and 99.6%, respectively. The vaccination-site reactions progressed faster for revaccinees than first-time vaccinees.**

*Conclusions:* **Simple-to-use telephone/Internet-based technology allowed detailed self-recording of response to smallpox vaccination among outpatients. Self-reports on site appearance were sufficient to determine vaccine takes in most vaccinees. During a mass vaccination event, an electronic monitoring system could facilitate tracking of vaccine reactions, including providing an early warning system for adverse events, and might reduce the burden associated with follow-up visits with healthcare professionals.**

The Department of Health and Human Services (DHHS) and the Centers for Disease Control and Prevention (CDC) have emphasized the importance of public health planning for bioterrorism events such as a smallpox attack and emerging infectious diseases such as pandemic flu. CDC cooperative agreements have required state public health departments to develop smallpox vaccination plans, and states are now being asked to develop plans for an influenza pandemic. In addition to the usual surveillance functions of health departments, these agencies may need to set up mass vaccination clinics, handle vaccine or prophylactic drugs, determine who should get vaccinated, and monitor clinical reactions to the vaccines.[1] However, few methods exist for real-time tracking of vaccinee experiences. The Vaccine Adverse Events Reporting System (VAERS) collects spontaneous

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reports of adverse events after vaccination, but VAERS does not actively solicit participants before vaccination, nor does it inform clinicians of the adverse events of their patients promptly after patients experience the event. Furthermore, it does not capture information on normal vaccine reactions.

In addition, data on the natural history of smallpox vaccination are dated, as the U.S. has not routinely vaccinated civilians against smallpox since 1972. Influenza vaccine reactions are better defined, although the implementation difficulties of the swine flu program of 1976 should remind planners of the importance of good monitoring. DHHS recently posted draft guidelines on preparing for and handling a pandemic influenza outbreak.[2] While vaccination for influenza is not as complicated as smallpox vaccination, the plan recognizes that adverse events will need to be tracked and reported in the case of an influenza pandemic.[2] It is not clear if VAERS will be sufficient for this purpose.

Recent advances in telephone and web-based data collection can streamline the process of monitoring vaccination reactions. Self-report of vaccination-site appearance and symptoms, if clinically accurate, could potentially provide an early warning of adverse reactions and, particularly for smallpox, obviate the need for paper diaries and the need for a postvaccination check with a healthcare provider and its attendant costs. We tested such a monitoring system during 2003 in the Department of Defense (DoD) smallpox vaccination program, replacing the CDC recommended[1] written diary of symptoms. Here we report the frequency of signs and symptoms reported by vaccinees and the sensitivity and specificity of using self-reports to determine successful vaccination. We also report on the natural progression of vaccine reaction in both naïve vaccinees and previously vaccinated individuals, because detailed objective data have not been available previously.

## METHODS

### *Subjects*

Institutional Review Board (IRB) approval for this research was obtained from the RAND Human Subjects Protection Committee, from the Abt Associates IRB, and from the IRBs at Brooke Army Medical Center and Walter Reed Army Medical Center.

Military personnel and civilian DoD employees slated to receive smallpox vaccine as part of the DoD vaccination program were invited to participate in the study. The study was conducted at four sites: Darnall Army Community Hospital, Fort Hood, Texas; Womack Army Medical Center, Fort Bragg, North Carolina; DeWitt Army Community Hospital, Fort Belvoir, Virginia; and the DiLorenzo Tricare Health Clinic at the Pentagon, Arlington, Virginia. Reports were received from March to September 2003.

Medical screening of the vaccinees and vaccination procedures are described elsewhere.[3] All vaccinees were asked to return to the clinic to have their vaccine sites checked 6–8 days after receiving the vaccination. At the point of vaccination, vaccine recipients were offered the opportunity to report vaccination signs and symptoms via an automated system developed by Voxiva Corporation (Washington, DC). Participation in the electronic monitoring system was entirely voluntary. Participants registered for the system and received instructions on its use, including a pocket-sized color brochure depicting expected vaccination-site responses. Beginning on the day of vaccination and continuing for 4 weeks, vaccine recipients were asked to call the telephone-based system or log in to the Internet web-based system to report the vaccination-site response and whether any signs or symptoms had occurred. To promote compliance, a call center was used to follow up with nonrespondents. At the start of the study, trained interviewers from the call center called vaccinees if they missed any daily report. Midway through the study, DoD requested a procedure change, and call frequency was reduced to calling vaccinees who had not reported on day 3, 6, or 9 postvaccination.

The automated, password-protected telephone system provided an audio introduction and then asked vaccinees to enter 2-digit codes for specific signs or symptoms. Alternately, vaccinees could log onto an Internet website to record corresponding data. All vaccinees had both reporting options. Participants who spoke with the call center could make reports directly to the call center staff.

Each vaccinee had the option to request contact with a nurse, using either the call center or the automated system; the nurse answered the vaccinee's questions and recommended referral to additional medical care if needed. Data from vaccinees whose reports contained triggers (e.g., reports of chest pain or extreme concern about their vaccine reaction) were automatically sent—by email, Short Message Service, or both—to the healthcare professional managing the vaccination process for that clinic, who then had responsibility for arranging follow-up for the vaccinee.

The following fixed-choice vaccination-site descriptions were used for vaccinees to report site reactions: none, colored spot (to identify macules), bump (to identify papules), reddish blister (to identify vesicles), whitish blister (to identify pustules), scab, scab fell off, unknown, and did not look. Vaccination-site symptoms included: itching, leaking fluid (to identify exudate), pain, local rash, streaking, swelling, warmth, and bandage reaction. Fixed choices for systemic signs or symp-

toms included: chest pain, chills, eye infection, feeling lousy, fever, headache, joint ache, muscle ache, rash (general), swollen lymph nodes, and other. Respondents could dictate or type in symptoms that were not listed.

### *Data*

When enrolling in the system, vaccinees provided information about their age, gender, race, military rank (E1–E9, W1–W5, O1–O9, or Civilian), and outpatient clinic. The clinic provided vaccination-response status and vaccination/revaccination status based on medical records. An analytic data set was created by merging the electronic monitoring system data set, including demographics and daily reports, with data from the DoD vaccination program.

Electronic reports were analyzed for site progression and compared with the health professional's assessment of vaccination response. The CDC definition of a take or "major reaction" is "a pustular lesion or an area of definite induration or congestion surrounding a central lesion, which can be a scab or an ulcer."[1] To maintain consistency with that definition, a "bump," "reddish blister," or "whitish blister" had to be reported in the electronic self-reports to be considered a take for purposes of this analysis. To be considered a nonresponder (nontake), a vaccinee had to make a report of "none" or "colored spot" at least once on or after day 6 after vaccination (the first day recommended by the World Health Organization [WHO] for take checks) without reporting further progression to bump, blister, or scab.

### *Statistical Methods*

We used Chi-square tests and two-sample *t*-tests to compare demographic characteristics across different population groups. To compare the incidence of specific symptom reporting between first-time vaccinees and revaccinees, logistic regression models were used. Negative binomial regression models were used to compare revaccinees and first-time vaccinees regarding total number of distinct symptoms. Similarly, for total number of symptoms per report, due to the skewed distribution of the reports, categories were formed and multinomial regression models were used. To compare timing of vaccine-site appearances and selected symptoms between revaccinees and first-time vaccinees, time-to-event models, specifically the Cox proportional hazards model, were used. All of these regression models included gender, race, outpatient clinic, military rank, and revaccination status as independent variables. Age could not be included in these models due to high collinearity with revaccination status. All statistical procedures were implemented using SAS (SAS System version 8.2, Cary, NC).

## RESULTS

### *Use of the System*

A total of 1,649 vaccinees volunteered to use the electronic monitoring system. Most were from Fort Hood ($n$ = 715) or the Pentagon ($n$ = 822). Unfortunately, because the system was implemented during the preparation for the war in Iraq, the number of people who were approached and declined to participate was not collected. Most of those who declined stated that they were deploying within a week and would not be able to fully participate. Demographic characteristics of volunteers from Forts Belvoir, Bragg, and Hood were similar and are reported in aggregate as "Army posts" (Table 1). Volunteers from the Pentagon were more likely to be officers,

TABLE 1. DEMOGRAPHICS OF VACCINEES BY CLINIC

| | *Army posts* | *Pentagon* |
|---|---|---|
| Number who signed up for system | 827 | 822 |
| Number who used the system | 546 (66%) | 708 (86%) |
| Mean number of reports (±SD) | 4.4 ± 5.0 | 8.6 ± 6.3 |
| Median number of reports | 2 | 7 |
| Mean age (±SD) | 28 ± 8 | 42 ± 9 |
| % Officer | 7.6 | 65 |
| % Enlisted/Warrant | 91 | 20 |
| % Civilian | 1.6 | 15 |
| % White[a] | 55 | 81 |
| % Black[a] | 26 | 11 |
| % Male | 93 | 87 |
| % Revaccinee | 30 | 87 |

[a]Race was categorized as white, black, or other.

Caucasian, revaccinees, and older. Of the 1,649 who enrolled in the electronic monitoring system, 1,254 (76.0%) used the system at least once, making a total of 8,510 electronic reports (Figure 1). The mean number of reports made per user was 6.8 ± 6.2 (mean ± SD), and the median number of reports was 5 (range 1–28).

### *Take Checks*

Of the 1,254 respondents, 530 vaccinees had both enough reports to interpret a take and had their health professional take check recorded in their DoD vaccination records (Table 2). The electronic take-check data have a sensitivity of 98.9% (521/527), specificity of 33.3% (1/3), positive predictive value of 99.6% (521/523), and negative predictive value of 14.3% (1/7). For this calculation, we have treated the DoD vaccine records as the gold standard. Making the requirements for a take more restrictive (at least reporting a blister or reporting a bump and itching) did not change these values. If respondents did not make enough electronic reports to adequately determine their take status (320 respondents), their data were considered "missing" electronic data. Similarly, in 499 cases, electronic data were available, but a take determination was not recorded in the DoD clinic vaccination records, and data were considered "missing."

The DoD take records and the interpretation of electronic reports do not match for 8 cases for whom both self-report and take-check data are available. Two vaccinees whose DoD records indicated the vaccine did not take had electronic reports that met the definition for take. In one of these two cases, the clinic's take check was probably performed before the recommended time frame of 6–8 days, in that on day 4 the vaccination site was read as "no take," but the vaccinee made an electronic report of a bump on day 5 and continued to report through the scab falling off. The other vaccinee also reported the full progression of site appearance, from bump through scab falling off, and the take check was performed on day 10. We were unable to determine why the health professional take assessment for this person does not match the electronic records. We suspect a data entry error, because the date of vaccination in the military health record does not match the date of vaccination in the electronic reporting system.

Six vaccinees made electronic reports that we defined as nontakes but clinical records indicated as a take. These

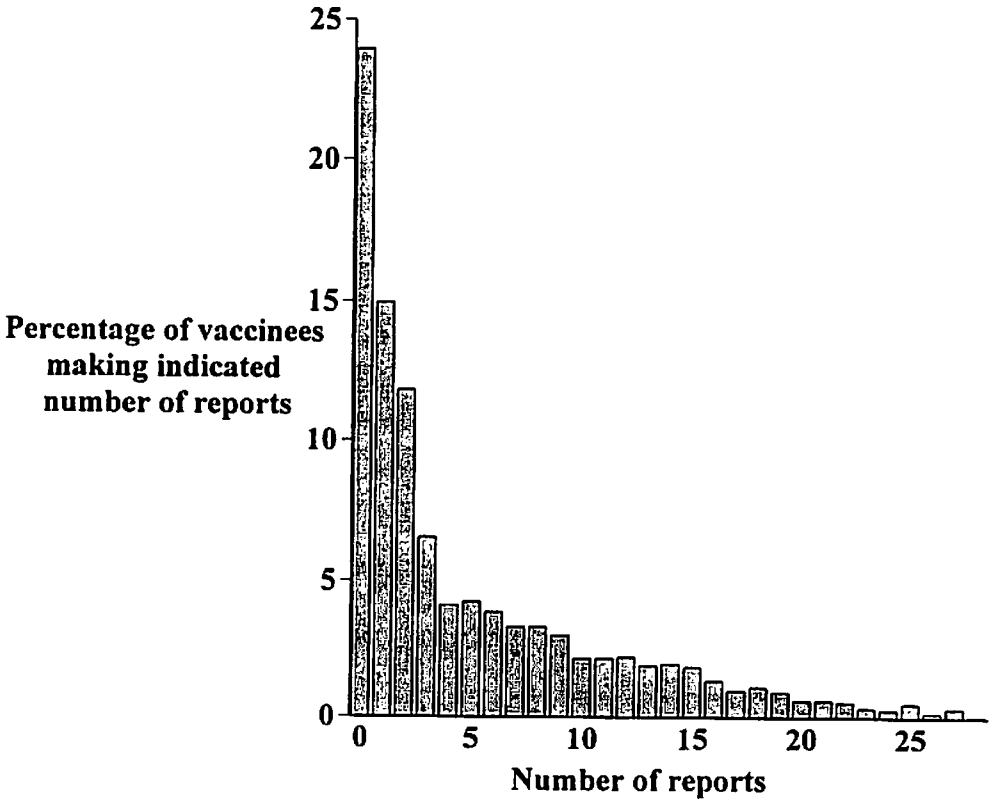


FIGURE 1. REPORTING RATES. The number of reports made by vaccinees is graphed as a percentage of vaccinees who signed up for the electronic monitoring system. The mean number of reports made per user was 6.8 ± 6.2 (mean ± SD), and the median number of reports was 5; 73.4% of reports were made on the web, 15.3% were made by calling into the system, and 11.3% were made directly by the call center.

TABLE 2. COMPARISON OF CLINIC TAKE-CHECK DECISIONS WITH ELECTRONIC DESCRIPTIONS EMPIRICALLY DEFINED AS A TAKE

| | | *Electronic reports* | | | |
|---|---|---|---|---|---|
| | | *Take* | *No take* | *Missing* | *Totals* |
| DoD | Take | 521 | 6 | 222 | 749 |
| Vaccine | No take | 2 | 1 | 3 | 6 |
| Records | Missing | 393 | 11 | 95 | 499 |
| | Totals | 916 | 18 | 320 | 1,254 |

6 vaccinees, 4 revaccinees and 2 first-time vaccinees, made an average of 4.5 electronic reports. None of the 6 reported anything other than none (no reaction) or colored spot, and all reported at least once on or after day 8, the last day recommended for a take check.

### *Progression of Vaccination Site and Symptoms*

Electronic records of vaccinees who had a take and whose vaccination/revaccination status was known were analyzed for progression of their vaccination site. We used only the first report of a specific site-appearance for each vaccinee to calculate this progression. A total of 1,683 reports from 245 first-time vaccinees and 6,191 reports from 661 revaccinees are included in this analysis (Figure 2). The average day of first report of the red blister, white blister, scab formation (all $p < 0.001$) and scab separation ($p = 0.02$) are all earlier for revaccinees than for first-time vaccinees.

The length of time that a scab persisted was often longer than the 21 days previously reported.[1] Of the 293 users who made electronic reports 21–28 days after getting vaccinated, 170 (58%) reported a scab during that time, including 30 (of 72) who reported a scab on day 28.

Symptoms were reported by 1,212 of the 1,254 system users. The frequencies of symptom reporting are summarized in Table 3. Users reported 3.8 ± 3.4 distinct symptoms (1.6 ± 1.9 symptoms per electronic report, mean ± SD). First-time vaccinees generally reported more distinct symptoms (4.3 vs. 3.6) and reported more symptoms per electronic report (2.2 vs. 1.3) than did revaccinees. The $p$ values listed in Table 3 comparing first-time vaccinees and revaccinees are from regression models that adjust for gender, race, clinic site, and rank. The most common symptoms reported are graphed by post-vaccination day in Figure 3. Itching was the most frequently reported symptom, peaking early during the first week. The rest of the symptoms peaked around days 6

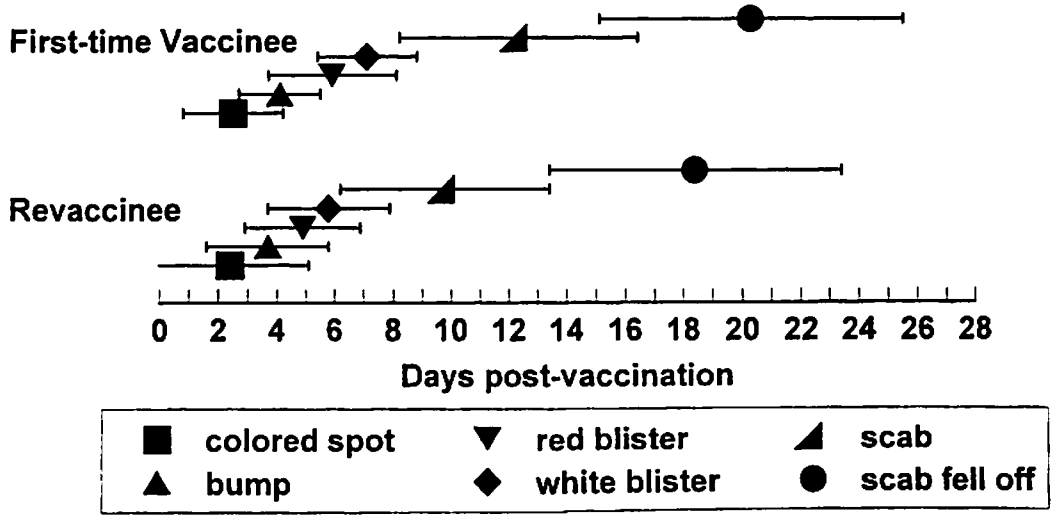


FIGURE 2. PROGRESSION OF VACCINE SITE APPEARANCE. Data are the mean (±SD) of the first day that vaccinees reported each site appearance. Results of time-to-event regression models indicate revaccinees report site progression earlier compared to first-time vaccinees: colored spot ($p = 0.06$), bump ($p = 0.13$), red blister, white blister, scab formation (all $p < 0.001$), scab separation ($p = 0.02$).

TABLE 3. COMPARISON OF REPORTED SYMPTOM DATA BY VACCINATION STATUS

| | *First-time vaccinee (n = 439)* | *Revaccinee (n = 773)* | |
|---|---|---|---|
| | *Mean (SD)* | *Mean (SD)* | *p-value*[a] |
| All symptoms | 9.5 (13.9) | 9.6 (12.2) | NA |
| All symptoms (per report) | 2.2 (2.4) | 1.3 (1.4) | 0.02 |
| All symptoms (distinct) | 4.3 (4.0) | 3.6 (3.0) | <0.001 |
| Incidence of site symptoms | Percentage | Percentage | |
| Itching | 69.0 | 84.7 | 0.07 |
| Leaking fluid | 43.5 | 44.4 | <0.01 |
| Pain | 32.3 | 21.2 | <0.01 |
| Local rash | 17.3 | 12.8 | 0.01 |
| Streaking | 4.3 | 2.1 | 0.19 |
| Swelling | 27.8 | 22.3 | 0.01 |
| Warmth | 15.0 | 13.1 | 0.08 |
| Bandage reaction | 34.4 | 23.0 | <0.01 |
| Incidence of other symptoms | | | |
| Chest pain | 5.2 | 2.3 | 0.46 |
| Chills | 12.1 | 6.1 | 0.05 |
| Eye infection | 0.7 | 0.6 | 0.61 |
| Feeling lousy | 32.8 | 24.2 | 0.01 |
| Fever | 12.8 | 5.8 | 0.01 |
| Headache | 29.8 | 24.1 | <0.01 |
| Joint ache | 18.2 | 12.9 | 0.07 |
| Muscle ache | 24.6 | 21.2 | 0.18 |
| Rash (general) | 4.6 | 3.8 | 0.34 |
| Swollen lymph nodes | 31.4 | 16.0 | <0.001 |
| Other | 16.6 | 16.0 | 0.14 |

[a]Comparisons are from regression models that adjust for gender, race, clinic site, and rank.

and 7 for revaccinees and days 8–10 for first-time vaccinees. As was the case with site progression, the average first day that most symptoms were reported was earlier for revaccinees than first-time vaccinees (joint ache, $p = 0.01$; itching, local rash, warmth, muscle ache, and swollen lymph nodes, $p < 0.01$; pain, leaking fluid, and swelling, $p < 0.001$).

Of the 1,254 users, 113 (9.0%) made at least one report that triggered an automatic message to a healthcare professional at their vaccination clinic. Forty-four vaccinees (3.5%) reported chest pain, and 77 (6.1%) reported being extremely concerned about their vaccination. The authors do not have follow-up information on the clinical course of these patients, but they were included in other surveillance efforts.[3]

## DISCUSSION

Advances in technology have the capacity to revolutionize both clinical care and public health. We found that recipients of smallpox vaccine were able to accurately assess their reaction to smallpox vaccine and to report it using telephone- and web-based technology. We believe that such emerging technologies can play an important role in the consideration of future vaccination campaigns. Even putting bioterrorism aside, it is not unlikely that a novel infectious disease or pandemic flu will emerge as a major public health challenge in the future and that a large vaccination campaign could be required.

Specifically with regard to smallpox, adverse events from the recent smallpox vaccination campaign have been documented for both the military and civilian populations.[3-6] In some cases, limited symptom data also have been reported.[3,7] However, other than a report of 48 vaccinees with potential superinfection,[8] this is the first detailed report of the progression of the vaccination site and symptoms, contrasting first-time vaccinees and revaccinees in this contemporary cohort. The vaccine reaction progressed more quickly in revaccinees than in first-

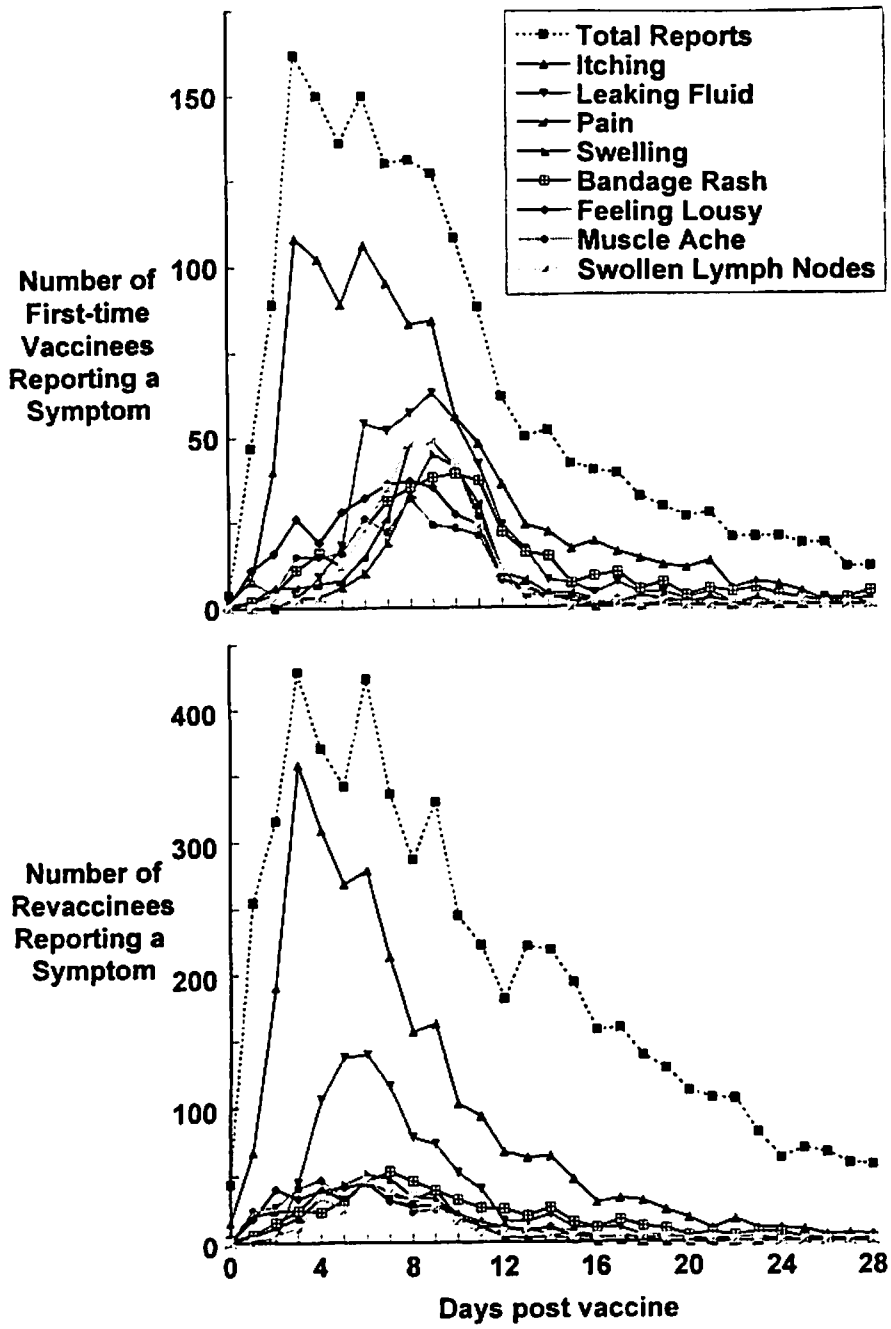


FIGURE 3. REPORTS OF SYMPTOMS BY POSTVACCINATION DAY FOR FIRST-TIME VACCINEES (UPPER GRAPH) AND REVACCINEES (LOWER GRAPH). First-time vaccinees made more reports of symptoms (both frequency of reporting and number of unique symptoms reported) than revaccinees. Itching was the most commonly reported symptom for both groups, peaking during the first week. The average first day that most symptoms were reported was significantly earlier for revaccinees than first-time vaccinees (see text for $p$ values).

time vaccinees, while first-time vaccinees were more likely to report symptoms including pain, rash, and swollen lymph nodes.

We found that overall use of the electronic monitoring system was modest but that the sensitivity and positive predictive value of self-report of a vaccine take was quite high. If the reporting frequency could be improved, clinics could rely on an electronic monitoring system to monitor vaccine take among their clients. With this cohort, the electronic system could have reduced the number of return take-check visits by 73%. In addition, the system is designed with the ability to automatically notify a

healthcare professional when a vaccinee reports a symptom of concern, such as chest pain.

There are several likely explanations for the relatively modest use of the system. First, the system began operation at the height of deployment in preparation for the war in Iraq, and it is likely that both the salience of reporting and access to telephones and/or the Internet were quite limited. In addition, unlike in a public health emergency where people would likely be focused on the emergency itself, vaccinees here were focused more on deployment to Iraq and the impending war than on their vaccination. However, we cannot predict whether other distractions will inhibit reporting. Further, this was a pilot study, and we expect that the recruitment and explanation process could be enhanced in ways that would increase the frequency and likelihood of reporting. This first test of the electronic system did not include automatic email reminders or incentives for reporting. Additional use of electronic reminders and modest incentives (e.g., a prepaid phone card) may increase frequency of reporting. Use of a call center was important in stimulating reporting, although it did not have the magnitude of effect we had hoped. However, based on the results of this pilot, we are able to identify groups at highest risk of not reporting and could target that subpopulation for intensive work by the call center.[9]

These results also reinforce the importance of performing the take check after sufficient time for the vaccination reaction to occur. On at least one occasion, a vaccinee returned for a take check on day 4 postvaccination, before the take was apparent physically. The vaccination site progressed to a white blister by day 6 and would probably have been correctly interpreted as a take at that time. Furthermore, the results suggest that the ideal time for a take check may start slightly earlier for revaccinees compared with first-time vaccinees.

Clinical experience passed down from the 1960s included the expectation that vaccinia scabs would fall off between the 14th and 21st days.[1] Our observation of longer scab-retention intervals could be due to greater use of bandages than was common in the 1960s, lack of an evidence basis for the 14–21 day interval, or both.

The smallpox vaccination reaction is known to be different in first-time vaccinees compared with revaccinees.[10] Our site-appearance and symptom results confirm this, with each stage after bump and each of the site-specific symptoms except bandage rash and streaking occurring significantly earlier in revaccinees than in first-time vaccinees. However, age and vaccination status (first-time or revaccination) are collinear variables, so we were unable to adjust for age in our models. Potentially, this faster maturation is due to the activation of memory cells in the individual's immune system.[11] However, other biological and nonbiological explanations may account for the faster progression as well. In this study, older people, who are the ones more likely to have been previously vaccinated, made more reports with the system. The potential therefore exists for a bias based on the frequency of reporting. Older vaccinees may have been more likely to report the first day that their vaccination site changed appearance, which would give the appearance of having an earlier transition to the next stage, whereas younger vaccinees, who reported less frequently per capita, may not have reported on the first day that the vaccination site changed appearance.

Finally, revaccinees received 15 sticks with the bifurcated needle, while first-time vaccinees received 3 sticks, per the FDA-licensed dosing guidelines. We do not know whether 15 sticks in first-time vaccinees would have induced a faster immune response, either because a larger dose of vaccine was delivered or because more local trauma caused a greater inflammatory response, which may have caused a faster progression of the vaccination sites.

This electronic monitoring system was successful in gathering data from smallpox vaccine recipients. Although usage was modest, the data suggest that even modest usage during a mass vaccination campaign of the general public could facilitate tracking vaccine reactions, including providing an early warning system for adverse events and reducing the time associated with follow-up visits with healthcare professionals. For smallpox vaccinees, reporting just 2–3 times during the first 10 days postvaccination would provide enough information to demonstrate successful vaccination in most cases.

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