MAJOR ARTICLE

Safety Profile of Smallpox Vaccine: Insights from the Laboratory Worker Smallpox Vaccination Program

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Background. The frequency of mild-to-moderate adverse events following smallpox vaccination was not well documented or reported during the pre-eradication era. This report describes the frequency of such symptoms among 936 adult smallpox vaccinees with and without a history of prior smallpox vaccination.

Methods. Diary cards were distributed to 1006 laboratory workers and members of the Centers for Disease Control and Prevention (CDC) smallpox response team who received smallpox vaccination under an investigational new drug protocol during 2001–2002. Vaccinees were requested to complete the diary card daily and return it to the CDC 28 days after vaccination. The proportion of vaccinees reporting symptoms was determined and compared among subgroups.

Results. Ninety-three percent of the diary cards were returned. The most common symptom reported was "itching at vaccination site." Primary vaccines reported statistically higher proportions of the following 11 symptoms: joint pain (25% vs. 11%; $P = .0011$), muscle pain (46% vs. 19%; $P < .0001$), fatigue (43% vs. 29%; $P = .0161$), swelling at vaccination site (58% vs. 33%; $P < .0001$), itching on the body (31% vs. 17%; $P = .0048$), abdominal pain (11% vs. 2%; $P = .0012$), swollen or tender lymph nodes (71% vs. 33%; $P < .0001$), pain at injection site (48% vs. 30%; $P = .0018$), headache (40% vs. 25%; $P = .0088$), backache (17% vs. 7%; $P = .0090$), and fever (temperature, ≥100°F [37.7°C]; 20% vs. 9%; $P = .0047$).

Conclusions. This analysis suggests that previously unvaccinated persons aged <30 years experienced more symptoms than did previously vaccinated persons. The findings of increased proportions with joint pain, abdominal pain, backache, and difficulty breathing were unexpected. As with recently described cardiac adverse events, these symptoms are suggestive of systemic involvement and warrant further study.

Recent concerns about the threats posed by bioterrorism [1, 2] have resulted in targeted smallpox vaccination programs for US civilian and military populations [1–4]. Before this Pre-Event Preparedness Program, the only recipients of the smallpox vaccine in the United States were a limited number of investigators [5–7] being vaccinated because of research activities involving reconstituted vaccinia virus as a vector [7]. Because the popularization of the smallpox vaccine by Jenner occurred before the introduction of modern clinical trials, there are relatively sparse data available on mild-to-moderate adverse events [8].

The Centers for Disease Control and Prevention (CDC) Drug Service has supplied vaccinia virus vaccine against smallpox (variola) to laboratory workers conducting research with vaccinia virus since the end of the smallpox eradication campaign in the early 1980s [5–7]. Dryvax (Wyeth Laboratories), the vaccine supply used for this purpose, consists of lots originally manufactured by Wyeth Laboratories in the late 1970s and early 1980s. In 2001, a formulation change in the diluents and a packaging change necessitated the use of this product under an investigational new drug (IND) protocol (2001-20C) until review and relicensure by the US Food and Drug Administration, which was completed in early 2003. Under the IND, diary cards for short-term adverse events were completed by the vaccinees and returned to the CDC for review. By use of the diary cards, we assessed the frequency of mild-to-

Received 10 August 2004; accepted 3 December 2004; electronically published 16 March 2005.

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Clinical Infectious Diseases 2005; 40:1133–40

1058-4838/2005/4008-0010

moderate symptoms following smallpox vaccination of several hundred persons vaccinated as part of the laboratory worker vaccination program or as smallpox response team members vaccinated before the Pre-Event Preparedness Program.

METHODS

Vaccine and diluent. The vaccine supply consisted of 3 primary components (Wyeth Laboratories): multiple lots of 100-dose vials of smallpox vaccine containing the New York City Board of Health vaccinia virus strain that had been produced before 1983 (Dryvax; Wyeth Laboratories) and stored at −20°C; vaccine diluent (a solution of 50% glycerin, 0.21% phenol, and sterile water for injection; Chesapeake Biological Laboratories); and bifurcated needles for administration.

The CDC Drug Service received requests for smallpox vaccine from laboratory researchers investigating vaccinia virus, as well as from other persons and institutions. If the request fell within program guidelines, the vaccine, diluent, bifurcated needles, and IND protocol documentation were shipped to the requestor and administered by trained personnel. All records of vaccination and documentation of responses to the vaccine were subsequently maintained by the CDC Drug Service.

Study population and diary cards. Smallpox vaccine reconstituted with this new diluent (ratio, 1:1) was administered to a cohort of 1006 persons under this IND from October 2001 through December 2002. The majority of vaccinees were research personnel at biomedical laboratories conducting research that used vaccinia virus as vectors. In addition, staff at vaccine manufacturers engaged in increasing the availability of smallpox vaccine and persons potentially exposed to orthopoxviruses were included in this cohort. Also among the vaccinees were members of the CDC smallpox response teams ($n = 191$).

Vaccinees received diary cards to aid monitoring of adverse events. Three slightly different versions of the diary card were developed and used during the study period to address the evolving need for selected information. Each version collected basic demographic information and information about follow-up medical care. Information on symptoms was collected by use of check-off boxes for each symptom on each day after vaccination. For fever, participants were requested to record the temperature. Only version 1 collected information about smallpox vaccination history and the subject's medical history; this information was not collected on the later versions because of privacy concerns. Versions 2 and 3 were enhanced to collect information after postvaccination week 3 and to collect additional information about local reactions at the vaccine site by use of check-off boxes similar to those for previously collected symptoms. These additional local reactions are listed in table 1. Smallpox vaccination history for vaccinees who used versions 2 or 3 was obtained by matching to a roster of smallpox vaccinees with either the first and last name or social security number. Date of vaccination was also used for subjects with multiple vaccination records.

Analysis. Information recorded in diary cards was entered into a database at CDC for analysis. Data for versions 2 and 3 were analyzed collectively and separately from version 1 because of differences in the collection instrument as well as differences in the age, sex, and vaccination history of the subject population. Although included in tables 1 and 2, the data for vaccine site lesion reports of "pimple," "vesicle," "ulcer," "scab," and "redness" are not included in the analysis, because the symptoms are typically expected for a successful vaccination. After those symptoms associated with successful vaccinations were excluded, the number of symptoms reported by each subject for each diary day was determined. Time frames of interest were selected as days 0 (day of vaccination), 1, 2, 3–7, 8–14, 15–20, and 21–28 (version 2 and 3 only). The proportion of subjects reporting each symptom at least once per time frame was determined. For example, if a subject reported temperature of ⩾100°F (37.7°C; hereafter, "fever of ⩾100°F") on days 6, 7, and 8, that subject would be positive for fever for the time frames of "days 3–7" and "days 8–14."

The proportions of persons reporting a symptom at least once during days 0–20 were compared by sex, age group, vaccination history, and diary card version. Bivariate comparisons of diary card version, sex, age group, and vaccination history were analyzed by Fisher's exact test for proportions. To adjust for potential confounding between diary card versions, sex, and age, multivariate comparisons were conducted through logistic regression with use of a specific symptom as the dependent variable.

RESULTS

Descriptive epidemiology. Of the 1006 diary cards distributed, 936 (93%) were returned; 122, 480, and 334 subjects completed versions 1, 2, and 3, respectively. Sex and age were provided on 905 diary cards; 53% of participants were men. Most vaccinees (47%) were >40 years old, 27% were 31–40 years, and 26% were 18–30 years.

The distribution of subjects reporting 0, 1, 2, 3, 4, and ⩾5 symptoms each diary day is shown in figure 1. The proportion of subjects reporting no symptoms decreased from 85% on day 0 to 27% by day 3. From day 3 to day 7, the proportion of subjects reporting no symptoms remained <35%. From day 8 to day 20, the proportion steadily increased each diary day to 88%. During week 4 of observation, 94% of subjects (version 2 or 3) reported no symptoms.

For most symptoms, the proportion of subjects reporting a symptom increased from day 0 to days 3–7. Beginning with days 8–14, the proportion of subjects reporting the symptom generally decreased (table 1). For other symptoms—such as

Table 1. Frequency of symptoms following smallpox vaccination among 936 adult smallpox vaccinees.

	No. (%) of subjects who reported symptom at least once, by day after vaccination							
Symptom	0	1	2	3–7	8–14	15–20	>21	Days 0–20
Fever of ⩾100°F[a]	3 (0.3)	12 (1.3)	23 (2.5)	73 (7.8)	51 (5.4)	6 (0.6)	1 (0.1)	110 (11.8)
Chills	6 (0.6)	9 (1.0)	23 (2.5)	89 (9.5)	50 (5.3)	6 (0.6)	0 (0)	138 (14.7)
Joint pain	6 (0.6)	19 (2.0)	24 (2.6)	97 (10.4)	66 (7.1)	9 (1.0)	1 (0.1)	141 (15.1)
Muscle pain	32 (3.4)	50 (5.3)	57 (6.1)	162 (17.3)	98 (10.5)	11 (1.2)	2 (0.2)	232 (24.8)
Fatigue	24 (2.6)	58 (6.2)	60 (6.4)	219 (23.4)	123 (13.1)	21 (2.2)	4 (0.5)	295 (31.5)
Loss of appetite	3 (0.3)	10 (1.1)	18 (1.9)	55 (5.9)	42 (4.5)	2 (0.2)	0 (0)	87 (9.3)
Cough	5 (0.5)	14 (1.5)	16 (1.7)	49 (5.2)	41 (4.4)	7 (0.7)	1 (0.1)	75 (8.0)
Swelling at vaccination site	13 (1.4)	55 (5.9)	126 (13.5)	389 (41.6)	265 (28.3)	40 (4.3)	3 (0.4)	467 (49.9)
Swollen or tender lymph nodes	4 (0.4)	15 (1.6)	25 (2.7)	330 (35.3)	229 (24.5)	22 (2.4)	4 (0.5)	380 (40.6)
Itching at vaccination site	32 (3.4)	157 (16.8)	377 (40.3)	744 (79.5)	433 (46.3)	176 (18.8)	32 (3.9)	806 (86.1)
Itching on body	10 (1.1)	32 (3.4)	57 (6.1)	116 (12.4)	63 (6.7)	22 (2.4)	4 (0.5)	167 (17.8)
Pain at vaccination site	40 (4.3)	65 (6.9)	80 (8.5)	266 (28.4)	212 (22.6)	25 (2.7)	2 (0.2)	358 (38.2)
Headache	29 (3.1)	47 (5.0)	38 (4.1)	179 (19.1)	121 (12.9)	24 (2.6)	3 (0.4)	266 (28.4)
Backache	4 (0.4)	13 (1.4)	10 (1.1)	51 (5.4)	44 (4.7)	6 (0.6)	0 (0)	84 (9.0)
Abdominal pain	0 (0)	4 (0.4)	6 (0.6)	19 (2.0)	9 (1.0)	3 (0.3)	1 (0.1)	29 (3.1)
Difficulty breathing	0 (0)	4 (0.4)	4 (0.4)	13 (1.4)	5 (0.5)	1 (0.1)	0 (0)	18 (1.9)
Vaccine site lesion[b]								
Pimple	37 (4.0)	137 (14.6)	229 (24.5)	376 (40.2)	48 (5.1)	12 (1.3)	1 (0.1)	520 (55.6)
Vesicle	4 (0.4)	10 (1.1)	62 (6.6)	564 (60.3)	256 (27.4)	24 (2.6)	4 (0.5)	599 (64.0)
Ulcer	1 (0.1)	1 (0.1)	6 (0.6)	252 (26.9)	255 (27.2)	57 (6.1)	8 (1.0)	378 (40.4)
Scab	1 (0.1)	1 (0.1)	4 (0.4)	170 (18.2)	535 (57.2)	448 (47.9)	136 (16.7)	618 (66.0)
Size of >3 inches (7.6 cm)	1 (0.1)	1 (0.1)	4 (0.4)	24 (2.6)	33 (3.5)	5 (0.5)	1 (0.1)	47 (5.0)
Redness	117 (12.5)	249 (26.6)	335 (35.8)	542 (57.9)	412 (44.0)	124 (13.2)	31 (3.8)	627 (67.0)
Swelling	10 (1.1)	34 (3.6)	84 (9.0)	294 (31.4)	199 (21.3)	23 (2.5)	1 (0.1)	361 (38.6)
Warmth	18 (1.9)	22 (2.4)	46 (4.9)	156 (16.7)	112 (12.0)	12 (1.3)	1 (0.1)	225 (24.0)
Pain	19 (2.0)	24 (2.6)	35 (3.7)	151 (16.1)	127 (13.6)	14 (1.5)	2 (0.2)	208 (22.2)
Streaks on arm	4 (0.4)	3 (0.3)	1 (0.1)	17 (1.8)	27 (2.9)	4 (0.4)	1 (0.1)	42 (4.5)
Rash on body	1 (0.1)	1 (0.1)	2 (0.2)	16 (1.7)	19 (2.0)	6 (0.6)	3 (0.4)	34 (3.6)
Vaccinia-type lesion elsewhere	0 (0)	2 (0.2)	2 (0.2)	10 (1.1)	12 (1.3)	8 (0.9)	1 (0.1)	20 (2.1)
Medical care sought[c]	NA	NA	NA	NA	NA	NA	NA	30 (3.2)
No. of symptoms reported[d]								
0	780 (83.3)	609 (65.1)	403 (43.1)	74 (7.9)	329 (35.1)	680 (72.6)	765 (94.0)	49 (5.2)
1	99 (10.6)	180 (19.2)	263 (28.1)	172 (18.4)	161 (17.2)	168 (17.9)	35 (4.3)	106 (11.3)
2	31 (3.3)	77 (8.2)	124 (13.2)	147 (15.7)	124 (13.2)	41 (4.4)	8 (1.0)	134 (14.3)
3	15 (1.6)	29 (3.1)	81 (8.7)	134 (14.3)	75 (8.0)	18 (1.9)	4 (0.5)	120 (12.8)
4	6 (0.6)	13 (1.4)	27 (2.9)	109 (11.6)	48 (5.1)	13 (1.4)	1 (0.1)	110 (11.8)
⩾5	5 (0.5)	28 (3.0)	38 (4.1)	300 (32.1)	199 (21.3)	16 (1.7)	1 (0.1)	417 (44.6)
Any symptoms without itch[d]	137 (14.6)	240 (25.6)	345 (36.9)	719 (76.8)	507 (54.2)	138 (14.7)	27 (3.3)	799 (85.4)
Total subjects with follow-up	936 (100.0)	936 (100.0)	936 (100.0)	936 (100.0)	936 (100.0)	936 (100.0)	814 (100.0)	936 (100.0)

NOTE. Reported symptoms are available only from day 0 to day 20 for version 1 of the collection instrument. NA, not available.

[a] "Fever ⩾100°F" was reported as a temperature of ⩾100°F, ⩾37.7°C, or "yes" within the time frame.

[b] Comparable vaccine site lesion symptoms were NA for version 1 of the collection instrument.

[c] Version 3 forms include only "medical care ever sought." Therefore, only medical care ever sought is included.

[d] Did not include vaccine site lesion reports of "pimple," "vesicle," "ulcer," "scab," or "redness."

vaccine site lesion reports (version 2 or 3 only) of ">3 inches" (7.6 cm) and "streaks on arm" as well as "vaccinia-type lesion elsewhere" (version 2 or 3 only), "rash on body" (version 2 or 3 only), "backache" (version 1 only), and "difficulty breathing" (version 1 only)—the proportion of subjects reporting these symptoms increased slightly or remained at a peak from days 3–7 to days 8–14 rather than decreasing.

The most common symptom reported was "itching at vaccination site" (table 1), which was reported by >80% of subjects. Other commonly reported symptoms include vaccine site lesion reports of warmth, swelling at the vaccination site, swollen or tender lymph nodes, headache, fatigue, pain at the vaccination site, and muscle pain

The proportion of subjects reporting each symptom was generally higher for version 2 or 3 than for version 1. When the proportion of symptoms reported during days 0–20 were compared, subjects who used version 2 or 3 reported significantly greater joint pain (16% vs. 8%; $P = .0210$), cough (9% vs. 3%;

Table 2. Frequency of symptoms following smallpox vaccination, by previous vaccination status and age group, version 2 and 3 only.

	Previously unvaccinated subjects, by age		Previously vaccinated subjects, by age	
Symptom	≤30 years	31–40 years	31–40 years	>40 years
Fever of >100°F[a]	14 (21.5)	4 (21.1)	4 (7.1)	13 (11.8)
Chills	13 (20.0)	3 (15.8)	6 (10.7)	13 (11.8)
Joint pain	15 (23.1)	7 (36.8)	7 (12.5)	12 (10.9)
Muscle pain	33 (50.8)	7 (36.8)	10 (17.9)	25 (22.7)
Fatigue	37 (56.9)	3 (15.8)	20 (35.7)	31 (28.2)
Loss of appetite	10 (15.4)	2 (10.5)	7 (12.5)	8 (7.3)
Cough	5 (7.7)	3 (15.8)	4 (7.1)	12 (10.9)
Swelling at vaccination site	41 (63.1)	8 (42.1)	28 (50.0)	51 (46.4)
Swollen or tender lymph nodes	48 (73.8)	11 (57.9)	23 (41.1)	27 (24.5)
Itching at vaccination site	60 (92.3)	18 (94.7)	47 (83.9)	95 (86.4)
Itching on body	24 (36.9)	5 (26.3)	17 (30.4)	24 (21.8)
Pain at vaccination site	34 (52.3)	7 (36.8)	21 (37.5)	27 (24.5)
Headache	28 (43.1)	6 (31.6)	13 (23.2)	25 (22.7)
Backache	13 (20.0)	3 (15.8)	4 (7.1)	7 (6.4)
Abdominal pain	9 (13.8)	1 (5.3)	1 (1.8)	3 (2.7)
Difficulty breathing	4 (6.2)	0 (0)	0 (0)	0 (0)
Vaccine site lesion				
Pimple	43 (66.2)	11 (57.9)	33 (58.9)	64 (58.2)
Vesicle	47 (72.3)	13 (68.4)	35 (62.5)	79 (71.8)
Ulcer	29 (44.6)	7 (36.8)	20 (35.7)	50 (45.5)
Scab	50 (76.9)	13 (68.4)	35 (62.5)	82 (74.5)
Size of >3 inches (7.6 cm)	4 (6.2)	1 (5.3)	2 (3.6)	10 (9.1)
Redness	49 (75.4)	13 (68.4)	42 (75.0)	79 (71.8)
Swelling	36 (55.4)	7 (36.8)	25 (44.6)	39 (35.5)
Warmth	27 (41.5)	4 (21.1)	15 (26.8)	38 (34.5)
Pain	23 (35.4)	5 (26.3)	16 (28.6)	18 (16.4)
Streaks on arm	6 (9.2)	1 (5.3)	2 (3.6)	7 (6.4)
Rash on body	3 (4.6)	2 (10.5)	2 (3.6)	3 (2.7)
Vaccinia-type lesion elsewhere	3 (4.6)	0 (0)	0 (0)	3 (2.7)
Medical care sought	2 (3.1)	1 (5.3)	0 (0)	1 (0.9)
No. of symptoms reported[b]				
0	0 (0)	0 (0)	5 (8.9)	8 (7.3)
1	1 (1.5)	2 (10.5)	7 (12.5)	13 (11.8)
2	5 (7.7)	3 (15.8)	6 (10.7)	20 (18.2)
3	2 (3.1)	3 (15.8)	6 (10.7)	9 (8.2)
4	8 (12.3)	3 (15.8)	7 (12.5)	19 (17.3)
≥5	49 (75.4)	8 (42.1)	25 (44.6)	41 (37.3)
Any symptoms without itch[b]	65 (100.0)	17 (89.5)	45 (80.4)	89 (80.9)
Total subjects with follow-up	65 (100.0)	19 (100.0)	56 (100.0)	110 (100.0)

NOTE. Data are no. (%) subjects who reported the symptom at least once from day 0 to day 20.

[a] "Fever ≥100°F" was reported as ≥100°F, ≥37.7°C, or "yes" within the time frame.

[b] Did not include vaccine site lesion reports of "pimple," "vesicle," "ulcer," "scab," or "redness."

$P = .0469$), swelling at vaccination site (56% vs. 12%; $P < .0001$), itching on body (20% vs. 5%; $P < .0001$), muscle pain (26% vs. 14%; $P = .0023$), and fever of ≥100°F (13% vs. 6%; $P = .0239$). Subjects who used version 1 reported seeking medical care more often (9% vs. 2%; $P < .0001$).

Female subjects were younger than male subjects (58% female subjects were aged ≤40 years, compared with 48% of male subjects; $P = .0095$). In addition, subjects reporting with version 2 and 3 were younger than subjects reporting with version 1. Overall, during days 1–20, vaccinees aged 18–30 years

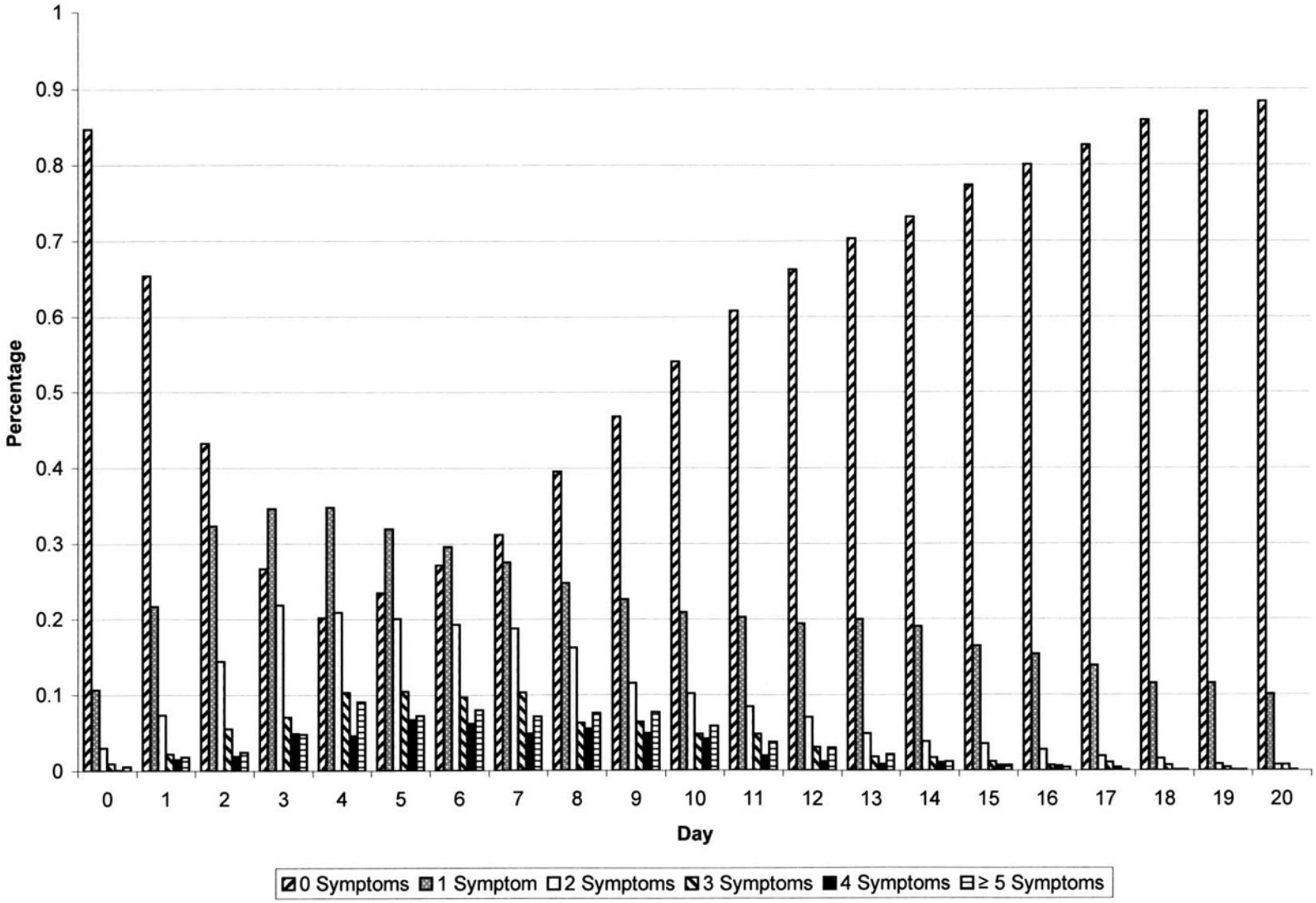

Figure 1. Percentage of subjects receiving smallpox vaccine who experienced symptoms for each diary day. All subjects were included regardless of diary card version and previous vaccination status.

were significantly more likely than subjects aged 31–40 years or subjects aged >40 years to report 14 symptoms, including chills (21% vs. 13% vs. 12%; $P = .0126$), joint pain (24% vs. 14% vs. 11%; $P < .0001$), muscle pain (39% vs. 23% vs. 18%; $P < .0001$), fatigue (45% vs. 32% vs. 25%; $P < .0001$), loss of appetite (13% vs. 10% vs. 7%; $P = .0498$), swelling at vaccination site (67% vs. 48% vs. 42%; $P < .0001$), swollen or tender lymph nodes (66% vs. 38% vs. 28%; $P < .0001$), itching on body (24% vs. 20% vs. 14%; $P = .0030$), pain at injection site (51% vs. 34% vs. 33%; $P < .0001$), headache (37% vs. 28% vs. 24%; $P = .0028$), backache (16% vs. 9% vs. 5%; $P < .0001$), abdominal pain (8% vs. 2% vs. 1%; $P < .0001$), difficulty breathing (4% vs. 3% vs. < 1%; $P = .0015$), and fever of ≥100°F (19% vs. 8% vs. 10%; $P < .0001$).

Sexes also varied significantly between versions. The proportion of men decreased for each successive version (version 1, 68%; version 2, 56%; version 3, 43%; $P < .0001$). Women were significantly more likely than men to report swollen or tender lymph nodes (45% vs. 37%; $P = .0253$), pain at the injection site (45% vs. 31%; $P < .0001$), and headache (32% vs. 25%; $P = .0323$).

Smallpox vaccination history was determined through 3 data sources: the diary card database and the 2 laboratory roster databases. Overall, 480 (51%) of the 936 laboratory records merged with the diary card database, including 87%, 44%, and 48% of versions 1, 2, and 3, respectively. From the diary card database, vaccination history was reported for 121 subjects from version 1. From the laboratory roster databases, smallpox vaccination was determined for 263 subjects. Of the 384 subjects with vaccination history, 289 (75%) reported previous vaccination (revaccinee), whereas 95 did not (primary vaccinee).

Age was strongly related to vaccination history. Among persons aged 18–30 years, 88% were unvaccinated previously. Among those aged 31–40 years, 21% were previously unvaccinated, whereas only 2% of those aged >40 years were previously unvaccinated.

The proportion of subjects reporting symptoms was determined for those with and without a history of smallpox vaccination. For those without a history of smallpox vaccination, the proportion reporting symptoms was statistically significantly higher than for those with a history of vaccination among 11 symptoms, including joint pain (25% vs. 11%; $P = .0011$), muscle pain (46% vs. 19%; $P < .0001$), fatigue (43% vs. 29%; $P = .0161$), swelling at vaccination site (58% vs. 33%; $P < .0001$), itching on the body (31% vs. 17%; $P = .0048$), abdominal pain (11% vs. 2%; $P = .0012$), swollen or tender lymph nodes (71% vs. 33%; $P < .0001$), pain at injection site (48% vs. 30%; $P = .0018$), headache (40% vs. 25%; $P = .0088$), backache (17% vs. 7%; $P = .0090$), and fever of ≥100°F (20% vs. 9%; $P = .0047$). For several other symptoms, the proportion of subjects reporting the symptom was higher but not statistically significant, including difficulty breathing (4% vs. 1%), itch at the injection site (92% vs. 84%), cough (11% vs. 7%), loss of appetite (14% vs. 8%), and chills (19% vs. 12%). For other symptoms, such as lesions elsewhere, rash on the body, and seeking medical care, no difference was noted.

Because age was strongly related to vaccination history, the effects of age and vaccination status were further analyzed (table 2). The proportions of subjects reporting each symptom at least once from day 0 to day 20 were compared among 4 subgroups: age of 18–30 years and not previously vaccinated, age of 31–40 years and not previously vaccinated, age of 31–40 years and previously vaccinated, and age of >40 years and previously vaccinated. Only subjects who used version 2 or 3 of the diary card were included to minimize confounding from diary card version. Previously unvaccinated subjects aged ≤30 years were more likely to report experiencing symptoms. The proportions of subjects reporting joint pain, muscle pain, fatigue, swollen or tender lymph nodes, pain at vaccination site, headache, backache, abdominal pain, and difficulty breathing were significantly different between subgroups.

Subjects who reported seeking medical care ($n = 30$) were more likely to report symptoms of chills (37% vs. 14%; $P = .0021$), joint pain (30% vs. 15%; $P = .0332$), muscle pain (57% vs. 24%; $P < .0001$), fatigue (57% vs. 31%; $P = .0044$), swollen or tender lymph nodes (63% vs. 40%; $P = .0132$), pain at the injection site (67% vs. 37%; $P = .0018$), headache (57% vs. 27%; $P = .0014$), rash on the body (17% vs. 3%; $P = .0035$), and vaccinia-type lesions elsewhere (13% vs. 2%; $P = .0029$).

Multivariate logistic model. Because age, sex, previous history of smallpox vaccination, and diary card version were interrelated, multivariate logistic models that included sex, version, and age or previous smallpox vaccination were constructed for each symptom. In the model with sex, version, and age, younger age was significantly related to the same symptoms as reported in the bivariate analysis. However, sex remained significantly related only to pain at the injection site, and diary card version remained significantly related only to swelling at vaccination site and itching on body. Similarly, subjects who used diary card version 1 were more likely to report seeking medical care.

For the model that included sex, diary card version, and smallpox vaccination history, again, vaccination history was related to the same symptoms as reported in the bivariate analysis except itching on body. Sex did not remain significantly related to any of the symptoms reported in the bivariate analysis except pain at injection site. Subjects who used diary card version 2 or 3 reported significantly greater itching on body, swelling at site, and muscle pain, whereas subjects who used diary card version 1 reported greater seeking of medical care.

DISCUSSION

Our observational study provides further insights into the reactogenicity of undiluted Dryvax, administered to a modern adult population with a diverse mix of subjects, including younger primary vaccinees as well as older revaccinees. Our study extends the findings about the prevalence of less serious symptoms following smallpox vaccination to older vaccinated adults. As might be anticipated, older revaccinees had milder reactions overall than were observed in younger previously unvaccinated adults. No severe outcomes were reported among any smallpox vaccine recipients in either age group during the 4 weeks after vaccination. By week 4, nearly all subjects reported no symptoms.

Furthermore, despite the lack of an unvaccinated control group, the availability of the older vaccinated group with a distinct different reactogenicity profile provides a reasonable, if imperfect, comparison group. The elevated rate of select symptoms, such as joint pain, abdominal pain, backache, and difficulty breathing, in young previously unvaccinated persons compared with previously vaccinated persons was unexpected. Notably, abdominal pain and difficulty breathing were almost exclusively reported among unvaccinated subjects under the age of 30 years.

Our findings complement the recent dilutional studies by Frey et al. [9], in which reactogenicity was reported for 665 previously unvaccinated young adults 18–32 years of age; no life-threatening adverse events were reported, but up to one-third reported that mild-to-moderate symptoms after vaccination resulted in missed school, work, or recreational activities or difficulty sleeping. Because our diary card collected data about a slightly different set of adverse events than did the study of Frey et al. [9], we were able to document a broader range of systemic effects elicited by the smallpox vaccine. Difficulty breathing was not reported by Frey et al. [9]. The proportion reporting nausea in their study [9] was similar to the proportion reporting abdominal pain in our study. However, nausea information was not systematically collected in our diary cards, although it was reported in the "comments" section by 3 persons. Those who reported abdominal pain and/or difficulty breathing were more likely to report a number of other symptoms, suggesting these symptoms were part of a larger clinical syndrome and not a reporting artifact.

Our study has certain limitations. The data from the diary card are self-reported. By use of this self-report mechanism, participants may be more likely to report experiencing symptoms, leading to an overestimate of nonsevere outcomes. Furthermore, persons not returning diary cards may be less likely to have experienced symptoms, again leading to an overestimate of nonsevere outcomes. However, 93% of those receiving vaccinations returned diary cards, minimizing any potential effect of nonreturned diary cards. In addition, slightly different versions of the diary card were distributed. The sex, age, and vaccination status of the vaccinated population changed with the version, leading to confounding between diary card version and vaccination status. Certain symptoms, such as seeking medical care, swelling at vaccination site, itching on body, and muscle pain, seemed to vary systematically by diary card version, even after adjustment for age, sex, or vaccination history when available. Unfortunately, smallpox vaccination history was not collected on later versions of the diary card, nor was matching with the roster data complete. Furthermore, age and vaccination status were highly correlated. Therefore, there is potential for residual confounding due to the correlation of diary card version, age, or previous vaccination status. Another limitation to interpreting our study is the lack of standard case definitions for each adverse event following immunizations elicited in our diary card. This makes interpretation of these safety data across individuals and smallpox vaccine studies extremely challenging. The recent Brighton Collaboration to develop standard case definitions for adverse events useful in both clinical trials and postmarketing surveillance should prevent similar problems in the future [10].

There are few published data on the frequency of mild-to-moderate symptoms following smallpox vaccinations, even though certain symptoms, such as reports of itching, pain, pimple, vesicle, redness, ulcer, and scab at the vaccination site, are expected for successful vaccination [8]. In countries such as the United States and United Kingdom, which stopped routine vaccinations in 1971 and 1972, respectively [11, 12], studies of vaccine safety focused on serious adverse events, such as death, postvaccinial encephalitis, progressive vaccinia, generalized vaccinia, erythema multiforme, inadvertent inoculation, and eczema vaccinatum [11, 12]. Somewhat unexpectedly, 2 months into the Pre-Event Preparedness Program, several cases of myocarditis, pericarditis, and acute cardiac deaths among recent smallpox vaccinees were reported [13–15]. This led to the temporary suspension of the program in several states [16] and prompted the Advisory Committee on Immunization Practices to develop deferral criteria for persons with risk factors for cardiac disease [17]. As with recently described cardiac adverse events, our unexpected findings of increased proportions of subjects with joint pain, abdominal pain, backache, and difficulty breathing are suggestive of systemic involvement and warrant further study.

In "post-industrial" societies, the population is generally risk-averse [18, 19]. Furthermore, within the immunization program, the successful near-elimination of many vaccine-preventable diseases through high coverage of efficacious vaccines has resulted in greater concerns about vaccine-induced risks or vaccine safety [18]. The current population receiving

smallpox vaccine also differs from that of the 1970s, with a higher proportion of adults who are primary vaccinees, persons with immune-compromising conditions, and possibly those with increased risk factors for cardiac disease. All of these factors combine to suggest that development of safer vaccines should be pursued and further expansion of pre-event smallpox vaccinations should be done cautiously.

Acknowledgments

We thank Mary McCauley for her insightful reading and helpful suggestions.

Financial support. This study was funded by and all authors are employees of the Department of Health and Human Services, Centers for Disease and Control and Prevention.

Conflicts of interest. All authors: no conflicts.

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