

Smallpox Manifestations and Survival during the Boston Epidemic of 1901 to 1903

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Clinical records of 243 patients with smallpox consecutively admitted to the Southampton Street smallpox hospital in Boston, Massachusetts, during the 1901–1903 epidemic were reviewed. Smallpox was divided into five categories of varying severity; 47% of patients had varioloid, a relatively mild form of the disease usually occurring in previously vaccinated individuals with incomplete immunity. Survival information is available for 206 patients, of whom 36 (17.5%) died. Vaccination status, disease severity, and age were associated with survival, whereas sex, birthplace,

and race were not. While full recovery often took weeks, most deaths occurred 7 to 14 days after the onset of symptoms, and all deaths occurred within 18 days of symptom onset. Smallpox was eradicated worldwide in 1977, but knowledge of the disease is essential because its cause, variola virus, is considered a potential biological weapon.

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A smallpox epidemic occurred in Boston, Massachusetts, from 1901 to 1903, with a total of 1596 reported cases and 270 deaths (17%) (1). Although more than 95% of reported smallpox cases in the United States during the 20th century—including over 200 000 cases in 1920 to 1921—were caused by a mild variety of the disease, variola minor, the Boston epidemic was caused by the classic variola major form (2, 3). The cutaneous manifestations caused by variola minor and variola major are similar; however, patients with variola minor have slightly smaller lesions that evolve more rapidly, do not usually become seriously ill, and have a mortality rate less than 1% (2, 3). Naturally occurring smallpox was eradicated in 1977, but awareness of the disease must be maintained because variola virus remains a potential bioterrorism agent (4–6). We describe clinical manifestations of smallpox during Boston's last major epidemic and analyze factors associated with survival among patients admitted to one hospital.

BACKGROUND

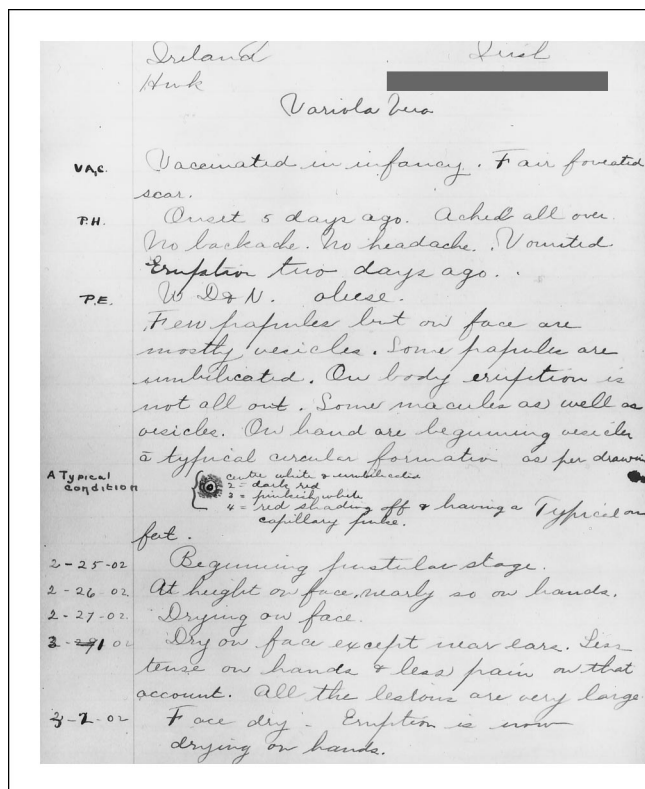
Because few physicians today have seen a case of smallpox, a summary of its clinical course is warranted. Smallpox is usually spread person-to-person in virus-laden droplets expelled from the oropharynx. The infection begins with seeding of the virus in the upper respiratory tract and regional lymph nodes, followed by involvement of the skin and internal organs (3, 7, 8). After a 7- to 17-day incubation period (mean, 10 to 12 days), clinical onset begins with a 3-day pre-eruptive stage that most commonly includes fever, malaise, headache, and backache. The exanthem generally starts on the face and spreads over the body in a centrifugal distribution, with greater involvement of the face and extremities than the trunk. A hallmark of the smallpox rash is its monomorphic appearance, with lesions appearing essentially as a single “crop” and evolving together through different stages as erythematous macules, papules, vesicles, pustules, and crusts. Vesicles often develop a central umbilication that persists into the pustular stage. The enanthem of smallpox appears as erythematous

macules that evolve into papules and vesicles and may involve the oropharynx, tongue, and nasal cavity. The rash resolves over 14 to 21 days, leaving disfiguring, pitted scars (with a predilection for the face) in more than half of typical cases of variola major. Complications of smallpox include encephalitis, pneumonitis, pneumonia, secondary cutaneous infection, arthritis, conjunctivitis, keratitis, and corneal ulceration (which can lead to blindness).

DETENTION OF PATIENTS WITH SMALLPOX DURING THE EPIDEMIC

All patients with smallpox in Boston during the epidemic, except those considered too sick to be moved from their homes, were detained at the Southampton Street or Gallop's Island hospitals, which were operated by the city of Boston (9–11). The Southampton Street smallpox hospital served as the major smallpox isolation and treatment facility. The Gallop's Island quarantine facilities, in Boston Harbor, were hastily expanded when additional beds were needed in the fall of 1901. Beginning in November 1901, a portion of men with smallpox were sent to Gallop's Island, either directly or by transfer from the Southampton Street hospital, if they “could be moved with safety” (9). Removal to Gallop's Island was historically objected to by many Bostonians because they associated Gallop's Island with neighboring penal institutions (12). Female and pediatric patients were treated at the Southampton Street smallpox hospital; however, one woman in this study was transferred to Gallop's Island with her husband. In 1902, 925 patients with smallpox were admitted to the Southampton Street smallpox hospital, with 142 of these subsequently transferred to Gallop's Island; 94 patients were directly admitted to Gallop's Island; and 5 patients remained at their homes (10). Milder cases tended to be sent to Gallop's Island. In 1902, the mortality rate was 11% at Gallop's Island compared with 20% at the Southampton Street smallpox hospital (10). Patients with smallpox were strictly excluded from all other hospitals in the city; early in the epidemic, the Boston City Hospital

Figure 1. An example of clinical notes.



Clinical records were compiled in a single, bound book. Demographic information, smallpox type, and vaccination history were recorded at the beginning of a patient's record (name, age, and marital status are not shown but were listed at the top of the page). The patient was a 43-year-old woman who was discharged "well" on 22 March 1902. (From clinical records of the Southampton Street smallpox hospital, Francis A. Countway Library of Medicine, Boston Medical Library, Boston.)

was temporarily quarantined when two inpatients developed the disease (13).

METHODS

Patient Records

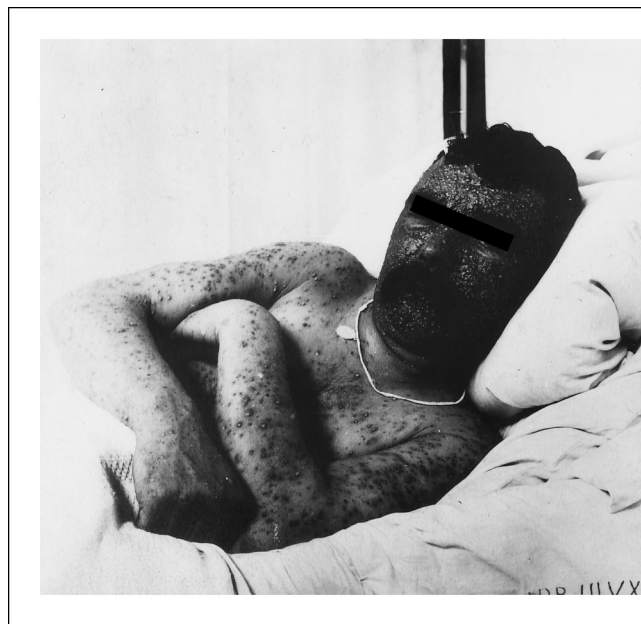
We reviewed clinical records of 243 patients with smallpox from the Boston epidemic. These patients were consecutively admitted to the Southampton Street smallpox hospital from 23 January to 3 April 1902. The medical records, recorded by Dr. Irving Reed Bancroft (1872–1963), are the only known existing records from the epidemic (Figure 1) (14). Dr. Bancroft, a 1900 graduate of Harvard Medical School, trained as the resident physician at the Southampton Street hospital during the epidemic, and he continued in a career in dermatology after the epidemic (15, 16). Records were obtained from the Boston Medical Library in the Francis A. Countway Library of Medicine, Boston, where they were donated in 1974. We excluded patients who did not have smallpox but were admitted for quarantine because of exposure and one patient who after admission was determined to have generalized vaccinia.

Statistical Analysis

The primary end point was survival duration, calculated as the number of days from onset of symptoms until discharge alive or death. The probability of survival was calculated by using the Kaplan–Meier method; survival curves were stratified by the following variables: type of vaccination ("successful," "unsuccessful," "recent 'primary,'" or "none"), disease severity, sex, age, race, or birthplace. In most instances, the confidence intervals for survival probabilities at various time points were computed by using the Rothman method (17). When there were no failures in a subgroup of patients, the exact binomial confidence was formed about 100%, based on the number remaining at risk at that time point. Patients who were discharged alive were treated as censored observations after the date of their last evaluation. The log-rank test for homogeneity among strata was used, with *P* values unadjusted for multiple comparisons.

Vaccination was interpreted as "successful" if it had been administered more than 3 weeks before admission and evidence of a scar or "take" was described; an "unsuccessful" vaccination left no scar; and "none" refers to patients with no history of vaccination. Patients with a "recent 'primary'" vaccination had no history of successful vaccination but were vaccinated within 3 weeks of admission. These patients were considered separately because they were likely infected at the time of their vaccination. Disease severity was defined as "mild" for varioloid cases, "intermediate" for variola vera cases, and "severe" for hem-

Figure 2. Day 7 of the varioloid form of smallpox in a 34-year-old man.



The patient had been successfully vaccinated in infancy and was discharged "well" 2 weeks later. (From clinical records of the Southampton Street smallpox hospital, Francis A. Countway Library of Medicine, Boston Medical Library, Boston.)

Figure 3. Day 8 of variola vera in a 3.5-year-old girl with an unidentified nurse at the Southampton Street smallpox hospital.



The patient had been unsuccessfully vaccinated 3 months before admission. Pustules appear in the same stage (monomorphic)—a characteristic feature of smallpox. She was discharged “well” 1 month later, although facial pitting was noted. (From clinical records of the Southampton Street smallpox hospital, Francis A. Countway Library of Medicine, Boston Medical Library, Boston.)

orrhagic disease. Race was considered black or nonblack. Birthplace was categorized as United States, Europe, or Canada (only two patients were categorized as “other” and were excluded from analyses involving birthplace). Thirty-three patients who were transferred to Gallop’s Island were excluded from survival analyses since all were transferred within 48 hours of admission and the outcome of their disease is unknown. In addition, one patient who died after secondary infection of her vaccination site (that is, not from smallpox) was excluded from smallpox survival analyses.

After univariate analysis (Kaplan–Meier curves with a log-rank test evaluation), Cox proportional hazards models (18) were constructed to determine which covariates were important with respect to survival when considered jointly. A likelihood ratio test was also performed to identify whether type of vaccination or disease severity were important factors in survival after adjustment for demographic characteristics identified as having potential importance. Statistical analyses were performed by using SAS software, version 8 (SAS Institute, Inc., Cary, North Carolina). All reported *P* values are two sided.

CLINICAL PRESENTATION

At the time of the epidemic, the standard practice was to divide cases into five clinical categories. *Varioloid*, or mild disease, usually occurred in patients with a history of successful vaccination that modified the clinical course (Figure 2). *Variola vera* was typical smallpox (Figures 3 to

5), and the severe hemorrhagic forms—*variola pustulosa hemorrhagica* and *purpura variolosa*—were marked by purpura. The two hemorrhagic forms were distinguished by whether the purpura preceded (*purpura variolosa*) or followed (*variola pustulosa hemorrhagica*) the skin eruption. *Variola sine eruptione* was defined as constitutional symptoms with few or no skin lesions (19).

Of 230 patients for whom the form of smallpox was listed, 109 had varioloid disease, 117 had variola vera, 3 had *variola pustulosa hemorrhagica*, and 1 had *purpura variolosa*. No patients were admitted with the diagnosis of *variola sine eruptione*. Eleven patients (7 with varioloid and 4 with variola vera) who had recently been vaccinated were given a concomitant diagnosis of “vaccinia,” a designation that appears to have included patients with smallpox who had only a localized reaction to the vaccinia vaccine.

Patients with varioloid at the Southampton Street smallpox hospital were described as having fewer and smaller or “aborted” lesions. A 27-year-old woman with a mild case of varioloid was described: “Very light papular eruption. Fifteen–twenty [lesions] only on face and less severe on body . . . No constitutional disturbances or temperature” (14). A 2.5-year-old girl with variola vera, who had been unsuccessfully vaccinated 2 months earlier, was

Figure 4. An unidentified nurse cleaning the eyes of a delirious 45-year-old man with variola vera (date of onset uncertain).



The patient had a history of successful vaccination in infancy. On discharge 1 month later, he was described as “well”: “weak on legs but is apparently mentally sound . . . has one discharging boil on legs.” (From clinical records of the Southampton Street smallpox hospital, Francis A. Countway Library of Medicine, Boston Medical Library, Boston.)

Figure 5. A 23-year-old unvaccinated woman with variola vera.



described at the time of admission as follows: “Eruption is severe and prostration is great. Eruption is now in late papular stage and is nearly confluent on face. Is sparse on body especially on abdomen and is thicker on legs but still not entirely confluent” (14). Two days later the rash had evolved: “Eruption is vesicular and early pustular. [Skin] [i]s broken down and is excoriated in many places.” Four days after admission, and 1 day before the patient died, Bancroft wrote: “Pustular and crusted on face. Face is swollen and eyes are closed. Pulse and temperature rising” (14).

Subsequent classification systems would be proposed for smallpox (3, 7). The classification system listed by the World Health Organization in 1988 divided the disease into five types: hemorrhagic (early and late forms), ordinary, modified, flat, and variola sine eruptione. This was similar to the classification system used at the time of the epidemic, the main difference being the inclusion of the severe flat type of the disease, postulated to reflect a deficient cellular immune response to the virus.

Complications described in the clinical notes included sepsis, lobar pneumonia, sublingual abscess, parotitis, conjunctivitis, iritis, keratitis, “septic” extremities or joints, skin abscesses, furunculosis, and “septic scales” (impetigo). After vaccination at the hospital, a newborn patient developed a “septic arm” that caused death. Documented laboratory abnormalities included albuminuria and leukocytosis; at times, the leukocyte count exceeded 30 000 cells/mm³.

RESULTS

Although we reviewed records from 243 consecutive patients, detailed information on individual characteristics was available in varying numbers of patients (Table 1). Sixty percent of patients were male, and the median patient age was 30 years. Blacks and immigrants made up 7% and 47% of the patient population, respectively. Seventy-three percent of patients had a history of vaccination before admission. The type of vaccination was determined for 234 patients, and 123 (53%) had evidence of successful vaccination. The type of vaccination and disease severity were indicated for 222 patients. Vaccination was successful in 84 of 105 (80%) varioloid cases, 32 of 113 (28%) variola vera cases, and 1 of 4 (25%) hemorrhagic cases. A history of vaccination and scar at the site were considered to represent successful vaccination; however, scars may have been acquired many years previously, with resultant diminished immunity.

Of 239 patients for whom discharge information was listed, 169 patients (71%) had recovered at discharge, 36 patients died (15%), and 33 adult patients (14%) were

The patient at day 4 (*top*), day 6 (*middle*), and day 11 (*bottom*) after the onset of illness. There appear to be purpuric lesions on days 6 and 11. A diagnosis of a hemorrhagic form of smallpox had been considered by staff shortly after admission. The patient died on day 12. (From clinical records of the Southampton Street smallpox hospital, Francis A. Countway Library of Medicine, Boston Medical Library, Boston.)

transferred to Gallop's Island within 48 hours of admission. All but 1 of the transferred patients were male, and they tended to have milder disease—19 of 26 (73%) were classified as varioloid and 7 of 26 (27%) as variola vera. One other patient, a 4-year-old boy who developed a “septic elbow joint” during his illness, was discharged with this condition at the request of his parents.

We performed survival analysis for nontransferred patients. Survival time was calculated from the date of symptom onset instead of the admission date because the former was considered a better reflection of the natural history of the disease; we excluded 17 patients whose time of symptom onset was not listed or was uncertain. These patients had a smaller 2-week probability of survival (55%) beginning from the date of admission than did all patients with or without information about symptom onset (81%). However, because the fraction of total patients who lacked onset information is small, overall actuarial survival at 2 weeks starting at admission only changed from 81% to

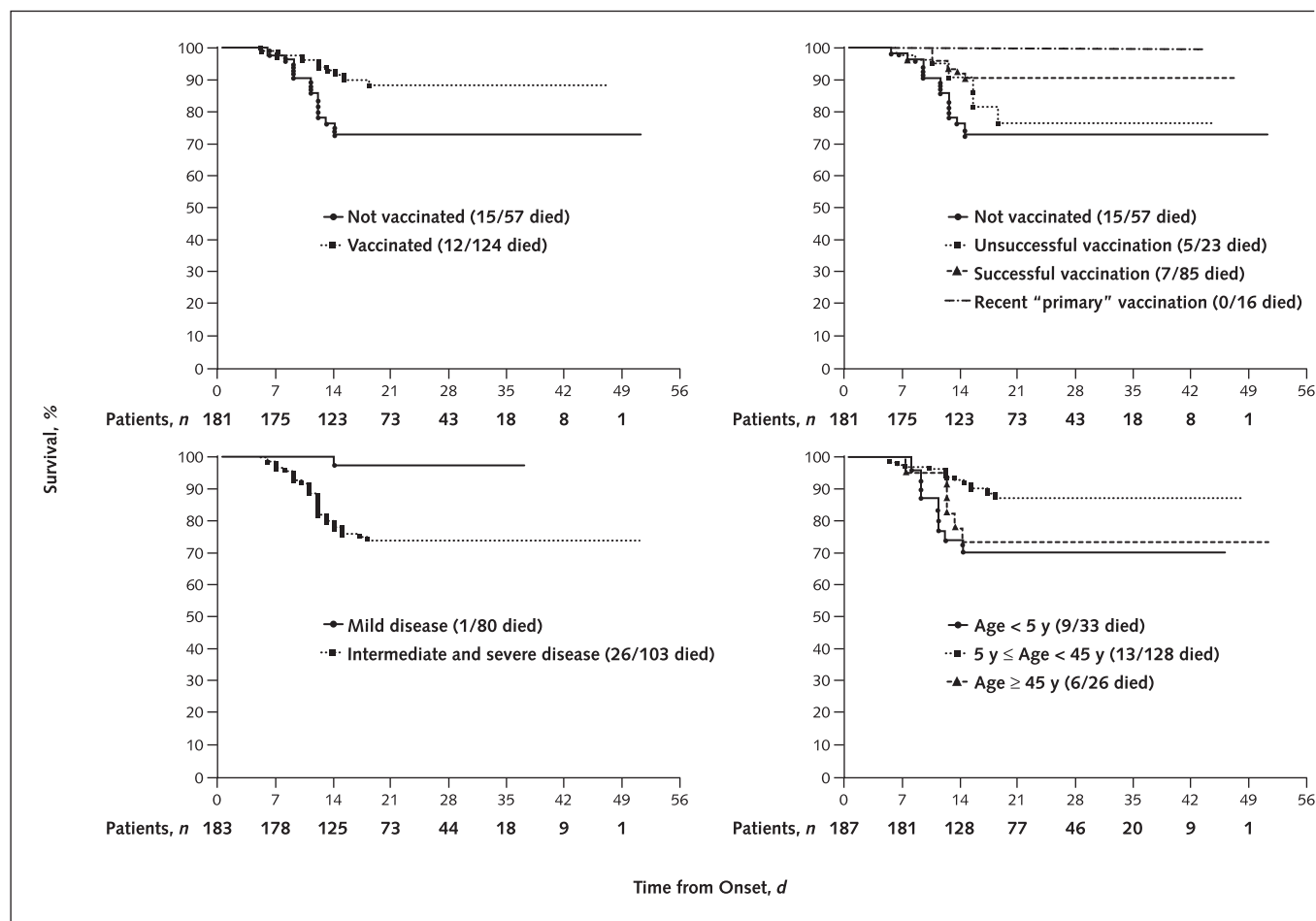
Table 1. Studied Variables and Number of Patients with Available Data (243 Total Patients)

Variable	Patients, n
Admission date	242
Sex	240
Age	240
Discharge status	239
Birthplace	238
Race	238
Discharge date	238
Disease severity	230
Date of symptom onset	222

83% by their exclusion. Furthermore, no significant association was found between the presence or absence of onset information and sex, birthplace, race, type of vaccination, disease severity, or age.

For the 188 patients with information on onset date and discharge status reported, the actuarial survival proba-

Figure 6. Survival of patients with smallpox from date of symptom onset.



Survival stratified by vaccination status ($P = 0.005$) (top left); type of vaccination (global $P = 0.012$; $P = 0.005$ for successful vs. none; $P = 0.034$ for recent primary vs. none) (top right); disease severity ($P < 0.001$) (bottom left); and age (global $P = 0.015$; $P = 0.008$ for patients younger than 5 years of age vs. patients 5 years of age or older and younger than 45 years of age; $P = 0.048$ for patients 45 years of age or older vs. patients 5 years of age or older and younger than 45 years of age) (bottom right). Symbols indicate deaths, and the numbers of patients at risk are indicated at 7-day intervals along the x-axis.

Table 2. Survival Probabilities at 14 and 21 Days from Disease Onset

Variable	Value	14-Day Survival Probability (95% CI), %	21-Day Survival Probability (95% CI), %	Overall P Value
Vaccination status	None	73 (60–83)	73 (60–83)	0.005
	Yes	92 (86–96)	89 (81–94)	
Vaccination type	None	73 (60–83)	73 (60–83)	0.012
	Unsuccessful	91 (73–98)	77 (56–90)	
	Successful	91 (83–96)	91 (83–96)	
	Recent “primary”	100 (75–100)	100 (72–100)	
Disease severity	Mild	98 (91–100)	98 (91–100)	<0.001
	Intermediate and severe	78 (70–85)	75 (65–82)	
Age	Age < 5 y	71 (54–84)	71 (54–84)	0.015
	Age ≥ 5 y and < 45 y	93 (87–96)	88 (81–93)	
	Age ≥ 45 y	74 (53–87)	74 (53–87)	

bility at 20 days was 84%. Seventy-nine percent of deaths occurred 7 to 14 days after the onset of symptoms, and all deaths occurred within 18 days. Patients with a history of vaccination had a higher probability of survival than patients who were not vaccinated (Figure 6, top left). At 14 days from symptom onset, the probability of survival for the group with vaccination was 92% (95% CI, 86% to 96%) compared with 73% (CI, 60% to 83%) for the patients who were not vaccinated. When vaccinated patients were further stratified by type of vaccination, those with successful vaccination or recent primary vaccination had a significantly higher probability of survival than those with no vaccination (Figure 6, top right). The probability of survival decreased with increasing disease severity (Figure 6, bottom left); only 1 of the 80 patients with complete data given a diagnosis of varioloid died. Patients younger than 5 years of age or 45 years of age or older had a lower probability of survival than patients in the middle age group (≥5 years and <45 years) (Figure 6, bottom right). Table 2 summarizes the 14- and 21-day survival probabilities and overall P values based on the variables of vaccination status, disease severity, and age. Survival was not statistically significantly associated with sex, birthplace, or race.

To assess the simultaneous importance of factors identified as being potentially prognostic by univariate analyses, we performed a stepwise Cox proportional hazards analysis. The following covariates were included in the analysis: vaccination status, disease severity, and age. The resulting model contained both disease severity and age as covariates

(with age <5 years and ≥45 years as higher-risk categories) (Table 3, model 1). A likelihood ratio test revealed that disease severity was significantly associated with survival after adjustment for age. A competing model containing vaccination status and age is also included in Table 3, model 2.

DISCUSSION

Analysis of clinical notes from the Boston smallpox epidemic of 1901 to 1903 reveals the broad variation in disease severity. Our study describes the effect that previous vaccination had on clinical presentation and survival. Patients with a history of vaccination were more likely to develop the relatively mild varioloid form of disease and had a higher probability of survival compared with patients who were not vaccinated. This suggests that while these patients had incomplete immunity and were susceptible to infection, vaccination could protect them somewhat by modifying disease severity. Also of interest are patients with a history of recent primary vaccination. These patients, who had no history of successful vaccination but had been vaccinated within 3 weeks of admission, had an increased probability of survival compared with patients who had never been vaccinated. Because vaccinia inoculated into the arm has a shorter incubation period (6 to 8 days) than variola virus acquired through respiratory inhalation, vaccination can alleviate or even abort smallpox if given soon after exposure (3, 20).

Age and disease severity were also associated with survival in our study. Infants and older patients were vulnerable to death from smallpox; patients younger than 5 years of age or 45 years of age or older had a lower probability of survival than those 5 years of age or older and younger than 45 years of age. Not surprisingly, disease severity was also associated with survival; patients with varioloid smallpox did better than those with variola vera or hemorrhagic disease.

Although analysis of a historical cohort from the Boston epidemic is informative, our study has obvious limita-

Table 3. Results of Cox Proportional Hazards Model Analysis

Model	Variable	Hazard Ratio (95% CI)	P Value
1	Disease severity (intermediate and severe vs. mild)*	17.13 (2.30–127.43)	0.005
	Age (<5 y vs. ≥5 y)	2.57 (1.08–6.12)	0.034
	Age (≥45 y vs. <45 y)	2.90 (1.09–7.74)	0.033
2	Vaccination status (no vs. yes)	3.20 (1.48–6.95)	0.003
	Age (≥45 y vs. <45 y)	2.64 (1.05–6.67)	0.040

* P < 0.001 for likelihood ratio test relative to age.

tions. The historical clinical notes seem to have been recorded consistently; however, this was not a controlled study, and we cannot be sure that the data do not contain potential sources of bias of which we are unaware. In addition, no information is available on the ultimate survival status after patients were discharged from the hospital alive. Patient records were available for only a portion of those who contracted smallpox in the epidemic. A larger study group might have indicated additional or different predictors of survival. Complete data were available for most but not all patients studied, and we had to exclude from survival analyses 33 adult patients (32 of whom were male) who were sent to Gallop's Island within 48 hours of admission. Transferred patients probably had a lower mortality rate than nontransferred patients since they tended to have varioloid cases; however, their outcomes are unknown.

The major concern about smallpox today is its possible reappearance as a biological weapon. Management at present would involve many of the same approaches used 100 years ago: reporting to local and national health authorities; isolation; treatment of symptoms and signs; and selective vaccination of patients and their contacts, medical staff, and the community. Specific treatment recommendations for patients with smallpox include strict respiratory and contact isolation, vaccination during the incubation period, maintenance of adequate nutrition and hydration, and systemic antibiotic therapy for secondary bacterial infection (21). The cytosine nucleotide analogue, cidofovir, approved for treating cytomegalovirus retinitis in AIDS, has been proposed as a potential therapeutic agent for smallpox. Because the threat of the deliberate release of variola virus is considered low, preexposure mass vaccination is not considered advisable (21). Adverse effects that may result from vaccination include autoinoculation, ocular vaccinia, generalized vaccinia, severe progressive vaccinia, erythema multiforme, eczema vaccinatum, and post-vaccinal encephalitis. Immunosuppressed persons are at particular risk for severe complications.

How would a smallpox epidemic today compare with that in Boston in 1901 to 1903? Clearly, many advantages in managing a smallpox epidemic exist today compared to a century ago. In addition to obvious therapeutic advances in supportive care and treatment of secondary bacterial infection, we have the benefits of regulation of vaccine production and quality, a more developed state and national public health infrastructure, greater federal support, and the experience of the World Health Organization's global Smallpox Eradication Program of the 1960s and 1970s. One hopes that there would be greater regard for civil liberties and ethical considerations than occurred during the Boston epidemic (1).

On the downside, we would share some of the same problems faced in the 1901–1903 epidemic. The lack of familiarity with smallpox among physicians is a concern, which was true in Boston in 1901 (22). Of greater impor-

tance is the fact that today most populations are unvaccinated and, thus, would be susceptible to infection. Similarly, when the Boston epidemic began, "the larger portion of the people were in a receptive condition for the disease," and 485 000 vaccinations were administered (mostly by family physicians and private agencies) by the end of 1901 (9).

Unlike 100 years ago, cases of smallpox are a hypothetical concern for us at present. Nonetheless, the threat of variola virus as a potential bioterrorism agent is lessened by preparedness, including emergency guidelines from the Centers for Disease Control and Prevention; continued awareness of the disease by clinicians; the availability of large stocks of vaccine virus for use in the event of an outbreak; and ongoing research into antiviral drugs, novel vaccines, and tests for early diagnosis (20).

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