Development and Experience with an Algorithm to Evaluate Suspected Smallpox Cases in the United States, 2002–2004


Concerns that smallpox, an eradicated disease, might reappear because of a bioterror attack and limited experience with smallpox diagnosis in the United States prompted us to design a clinical algorithm. We used clinical features of classic smallpox to classify persons presenting with suspected smallpox rashes into 3 categories: those with high, those with moderate, and those with low risk of having smallpox. The classification guides subsequent diagnostic strategies, limiting smallpox laboratory testing to high-risk persons to minimize the number of false-positive test results. From January 2002 through June 2004, the Centers for Disease Control and Prevention (CDC) received 43 consultations regarding suspected smallpox cases. No patient was at high risk for having smallpox. One patient was tested for the presence of variola virus. Varicella was the diagnosis for 23 cases (53%). The algorithm worked well to guide clinical and public health responses to suspected smallpox cases. The poster is available from CDC, and an interactive version and laboratory protocol are available at http://www.bt.cdc.gov/agent/smallpox/diagnosis/riskalgorithm/index.asp. We recommend use of the algorithm in the United States and elsewhere.

The events of 11 September 2001 and the anthrax-laced letters sent through the US postal system afterwards raised concern about the possibility of terrorist attacks with other biological weapons. Smallpox virus is a potential biological weapon because of its associated infectiousness, morbidity, and mortality. The threat from a smallpox outbreak is compounded by low population immunity.

In the United States, where the last case occurred in 1949, experience with diagnosing smallpox is limited. To address the lack of experience in the medical community, a round-the-clock telephone consultation hotline was established in late 2001 by the Centers for Disease Control and Prevention (CDC) to provide support for diagnosis of cases of febrile rash illness suspected to be smallpox. Initially, calls were returned by staff experienced in smallpox diagnosis. In several cases, by the time the CDC was consulted, drastic measures (e.g., quarantine of the hospital and refusal to admit the patient) had already been taken.

Consequently, the CDC recognized the need for a simple, reliable algorithm for identifying patients at high risk of having smallpox that would (1) provide clear information about smallpox and other causes of febrile, vesicular/pustular rash illnesses likely to be confused with smallpox; and (2) limit laboratory testing for smallpox to persons with the greatest likelihood of having smallpox. Widespread smallpox testing, in the absence of disease, is likely to result in false-positive test results with unnecessary and alarming public health and security responses. In this article, we describe the biomedical basis for the algorithm’s design, the management and diagnosis of cases that the CDC provided consultation on,
limitations of the algorithm, and the impact of the algorithm’s use on smallpox preparedness in the United States.

DEVELOPING THE ALGORITHM FOR DIAGNOSING SMALLPOX

To develop the algorithm, we contacted experts in the diagnosis of smallpox, varicella, and other infectious diseases, as well as other federal agencies and professional societies whose members needed accurate, up-to-date information for diagnosing smallpox. We used smallpox literature and expert opinion to characterize the clinical presentation of disease based on the presentation of ordinary-type smallpox, the clinical type of variola major that accounted for ~90% of hospitalized patients among unvaccinated persons in the pre-eradication era [1–5]. Once smallpox has progressed to the vesicular or pustular stage (typically 4–5 days after rash onset), 3 characteristics are almost always present; we named these the “major criteria” (table 1). Other commonly reported characteristics we named the “minor criteria.” Because varicella was the rash illness most commonly misdiagnosed as smallpox during and after smallpox eradication, we sought to clearly differentiate the 2 diseases.

Major Criteria

The major criteria are as follows:

- Febrile prodrome 1–4 days before rash onset.
- Classic smallpox lesions (i.e., deep-seated, firm, round, well-circumscribed lesions).
- Lesions at the same stage of development.

**Febrile prodrome.** In the largest published case series of hospitalized patients with variola major in Bombay, India (6942 cases), 100% of the patients had prodromal fever characterized by abrupt onset of high fever (generally 38.9°C–40.6°C [102.0°F–105.1°F]) and other symptoms, including headache (90% of patients), backache (90%), chills (60%), vomiting (50%), and severe abdominal pain (13%) [1]. In a study of 1040 hospitalized patients with variola major in west Pakistan, the febrile prodrome lasted for ≥24 h in 95% of patients, for ≥48 h in 75% of patients, and for ≥96 h in 12% of patients [3]. Most patients were bedridden during the prodrome.

We defined the prodrome as a temperature of ≥38.4°C (≥101.1°F) with ≥1 of the following symptoms: prostration, headache, backache, chills, vomiting, or severe abdominal pain. This temperature was selected to ensure that adults who had been vaccinated years ago and who presented with a modified prodrome would be detected. Smallpox is not the only illness to present with fever and systemic complaints before rash onset; however, few other rash illnesses have the dramatic and debilitating prodrome characteristic of smallpox. In varicella, fever generally coincides with the rash’s onset [5, 6].

**Classic smallpox lesions.** In the fully developed, pustular stage, smallpox lesions are deep seated and firm, 7–10 mm in size, initially round, dome shaped, and well circumscribed, and they sometimes progress to appear umbilicated or confluent. Pustules are located deep in the epidermis, described as “rolling a pea under the skin” [2]. In contrast, fully developed varicella vesicles are superficial, appear to be delicate (“dew drop on a rose petal”), are smaller (diameter, 2–3 mm), are frequently irregular or elliptical in shape, and are surrounded by erythema [5, 6].

All lesions at the same stage of development. In smallpox, all lesions develop at the same rate in the same body area; therefore, on any one part of the body, lesions are at the same developmental stage. Varicella lesions develop “crops,” with new lesions appearing in the same areas as older lesions; on any one part of the body, macules, papules, vesicles, and crusted lesions can coexist.

Minor Criteria

The minor criteria are as follows:

- Centrifugal distribution of lesions.
- First lesions on the oral mucosa/palate, face, or forearms.
- Patient appears toxic or moribund.
- Slow evolution of lesions of 1–2 days per stage.
- Lesions on the palms and soles.

The most characteristic feature of smallpox is morphology of the lesions: 4 of the 5 minor criteria relate to the distribution or progression of the lesions. Although not unique to smallpox, most classic smallpox cases will have all of these clinical features, whereas few varicella cases will. The smallpox rash begins as an oral enanthem. The exanthem appears first on the face and then spreads rapidly to proximal extremities, the trunk, and then distal extremities, usually within 24 h. Varicella may also begin as an oral enanthem followed by a facial rash, but subsequent aspects of the rash differ. Smallpox lesions evolve slowly with each stage (macular, papular, vesicular, and pustular), developing over 1–2 days, whereas varicella lesions evolve rapidly, typically progressing from macule to vesicle to crust in <24 h [5]. Smallpox lesions are concentrated on the face and distal extremities (centrifugal distribution); varicella lesions are concentrated on the face and trunk (centripetal distribution). Finally, smallpox lesions commonly occur on the palms and soles; this is rare with varicella.

The fifth minor criterion relates to severity of constitutional symptoms. Patients with smallpox are almost always quite ill, appearing toxic or moribund. With onset of rash, the high prodromal temperature may decrease, although not to a normal temperature, and the patient may feel better. However, as lesions evolve into pustules, a secondary fever occurs that increases until the lesions reach maximum size. The patient’s condition may worsen—deaths commonly occur at this stage.
Table 1. Major and minor criteria for diagnosis of smallpox.

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<tr>
<th>Major smallpox criteria</th>
<th>Details</th>
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<tr>
<td>Febrile prodrome occurring 1–4 days before rash onset (temperature of ≥38.4°C [≥101.1°F] and ≥1 of the following symptoms: prostration, headache, backache, chills, vomiting, or severe abdominal pain)</td>
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<tr>
<td>Classic smallpox lesions (i.e., deep-seated, firm/hard, round, well-circumscribed vesicles or pustules; as they evolve, lesions may become umbilicated or confluent)</td>
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<tr>
<td>Lesions in same stage of development: on any one part of the body (e.g., the face or arm), all lesions are in the same stage of development (i.e., all are vesicles or all are pustules)</td>
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<table>
<thead>
<tr>
<th>Minor smallpox criteria</th>
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<tr>
<td>Centrifugal distribution: greatest concentration of lesions on face and distal extremities</td>
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<tr>
<td>First lesions on the oral mucosa/palate, face, or forearms</td>
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<tr>
<td>Patient appears toxic or moribund</td>
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<tr>
<td>Slow evolution: lesions evolve from macules to papules pustules over days (each stage lasts 1–2 days)</td>
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<tr>
<td>Lesions on the palms and soles</td>
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In contrast, only the most severe cases of varicella result in a similar toxic or moribund appearance.

Smallpox Risk Classification and Public Health Action
The algorithm was designed to classify persons presenting with an acute, generalized vesicular or pustular rash illness suspected to be smallpox into 3 risk groups (table 2) and to guide public health response (figure 1). For all patients with a potentially infectious generalized rash illness, the most important initial response is rapid institution of appropriate contact and respiratory precautions. Patients should be isolated with negative airflow, if available; persons entering the room should wear an N95 or higher respirator, gloves, and gown.

High-risk patients should be reported immediately and undergo laboratory testing for smallpox. Moderate-risk patients should be urgently evaluated to rule out smallpox by “ruling in” other causes of rash illness. Laboratory testing for low-risk patients depends on the clinical situation.

**High risk of smallpox.** Patients are at high risk if they have all 3 major criteria. Local and state public health officials and the CDC should be alerted and specimens should be collected immediately.

**Moderate risk of smallpox.** Patients are at moderate-risk if they (1) have a febrile prodrome and have either classic smallpox lesions or lesions at the same stage of development, or (2) have a febrile prodrome and ≥4 of the 5 minor criteria. Moderate-risk patients should be evaluated urgently by specialists in infectious diseases and/or dermatology. Digital photographs are useful for consultation. These persons should undergo testing and receive treatment for varicella or other conditions according to their clinical condition.

**Low risk of smallpox.** Patients are at low risk, regardless of the severity of their illness, if they have <4 of the minor smallpox criteria, with or without a febrile prodrome. These patients should be tested for varicella and other conditions as clinically indicated.

**LABORATORY TESTING TO SUPPORT THE ALGORITHM**
A laboratory and pathology testing algorithm is available at http://www.bt.cdc.gov/agent/smallpox/diagnosis/rashtestingprotocol.asp. Samples from high-risk patients should be split and sent to one of 23 Laboratory Response Network (LRN) laboratories for orthopoxvirus and variola screening and to the CDC for confirmatory testing. If laboratory testing is indicated for moderate-risk and low-risk patients, the highest priority is varicella zoster virus (VZV) testing to rule in varicella. The recommended rapid tests for this purpose, in increasing order of reliability, are electron microscopy, Tzanck smear, direct fluorescent antibody (DFA) assay, and real-time PCR testing. Serologic testing is not useful for rapid diagnostic purposes. Electron microscopy may be useful to differentiate herpesviruses and poxviruses. The Tzanck smear is not specific for varicella, because it detects all alphaherpesviruses. VZV DFA assays are agent-specific, simple, and commercially available, but reliability requires careful collection and prompt processing of specimens. The most sensitive and specific rapid assay for detection of VZV is real-time PCR, which is now available to all state health departments and LRN laboratories. All these tests provide results within hours. For patients with a suspected infectious etiology, if the results of VZV tests are negative, the next priority is testing for herpes simplex virus (HSV) types 1 and 2 (HSV-1 and HSV-2, respectively); many state laboratories conduct DFA and PCR tests for these agents. If VZV and HSV test results are negative, other probable conditions (such as allergic dermatitis, drug reactions, and erythema multiforme) are more likely to be diagnosed clinically, so a dermatology con-
sultation may be useful, with skin biopsy for histopathological examination in selected patients.

For patients who are not classified as being at high risk, unless implicated as a result of epidemiological or clinical presentation, there is no indication to use laboratory tests to screen for orthopoxviruses. Screening of low-risk or moderate-risk patients leads to false-positive results: with spiked samples, in-orthopoxviruses. Screening of low-risk or moderate-risk patients would lead to reversal of the decisions.

Full risk of smallpox (report immediately)
Febrile prodrome, and
Classic smallpox lesion, and
Lesions in same stage of development
Moderate risk of smallpox (urgent evaluation)
Febrile prodrome, and
One other major smallpox criterion, or
Febrile prodrome, and
≥4 minor smallpox criteria
Low risk of smallpox (manage as clinically indicated)
No febrile prodrome, or
Febrile prodrome, and
<4 minor smallpox criteria

EXPERIENCE WITH THE ALGORITHM FOR EVALUATING SUSPECTED CASES OF SMALLPOX

The algorithm was distributed nationwide during late 2001 and early 2002 in numerous formats (electronically on the CDC Web site and subsequently by a mass mailing to physicians). A satellite broadcast educated physicians and state and local health departments about smallpox and its management.

During the period of January 2002 through June 2004, CDC consulted on 43 patients with suspected smallpox. Calls came from Florida (5 patients), California (4), Georgia (4), New Jersey (3), Ohio (3), Virginia (3), Arkansas (2), Illinois (2), Indiana (2), Maryland (2), New York City (2), North Carolina (2), Texas (2), Alabama (1), Kentucky (1), Michigan (1), Pennsylvania (1), Utah (1), Wyoming (1), and Australia (1). The sources of calls were emergency/critical care providers (16 calls); subspecialty providers, including dermatologists and infectious disease specialists (9); state or local health department personnel (9); primary health care providers (6); and hospital laboratory director and other (2). Eleven patients (25.5%) with suspected smallpox were <18 years of age, 30 (70%) were 18–64 years of age, and 2 (4.5%) were ≥65 years of age.

No patient was classified as having a high risk of smallpox. After consultation, 8 patients (19%) were classified by the consulting professional in collaboration with the CDC rash illness on-call staff as having moderate risk, and 35 (81%) were classified as having a low risk of having smallpox (table 3). This initial assessment was revised within 24 h for 4 moderate-risk cases (2 varicella cases and 1 case each of eczema and drug reaction), which were determined to be low risk on the basis of reassessments and/or clinical evolution. Varicella was the most common diagnosis (23 patients [53%]), with 5 of 8 cases initially classified as moderate risk, and 18 of 35 cases initially classified as low risk. Two patients (1 child and 1 adult) with varicella who were initially classified having a low risk of smallpox died. One other case was diagnosed as disseminated herpes zoster. Thus, VZV infections occurred in 24 patients (56%). The other initially moderate-risk cases were diagnosed as being erythema multiforme, severe eczema, and drug reaction. Other diagnoses included disseminated infection HSV-1 and HSV-2, Stevens-Johnson syndrome, drug and allergic reactions, bacterial infections, and other dermatological diseases. Although not a patient with a high-risk case, one patient was tested for smallpox virus; the results were negative [8]. Hospital and emergency department closures and diversions occurred in 7 instances, but use of the algorithm with CDC guidance quickly led to reversal of the decisions.

Of the 43 cases, 27 diagnoses were established either by laboratory tests (16 cases) or pathological tests (11 cases; Tzanck smear for 2 and skin biopsy for 9). Several of the biopsy-diagnosed cases had negative Tzanck smear or VZV DFA test results prior to biopsy. Of the remaining 16 clinically diagnosed cases, 2 had nondiagnostic results (VZV serological tests), and 3 had negative results that were useful in guiding further management. The 16 laboratory-confirmed cases were varicella (14 cases) and HSV-1 and HSV-2 infection (1 case each). Electron microscopy confirmed the presence of a herpes virus in a patient with positive VZV DFA test result. Pathological testing confirmed 2 cases of varicella (by Tzanck smear) and most of the noninfectious cases (by examination of skin biopsy specimens), including erythema multiforme, Gianotti-Crosti syndrome, Behcet disease, and drug reactions.

DISCUSSION

With use of the rash algorithm, no patients reported to the CDC consultation hotline for suspected smallpox during the period of 2002 through June 2004 were classified as being at high risk of having smallpox. From September through De-
Figure 1. Algorithm for the evaluation of patients with acute, generalized vesicular, or pustular rash illness whose cases raise suspicion of smallpox, for use in the absence of confirmed circulation of smallpox virus. CDC, Centers for Disease Control and Prevention; derm, dermatology; ID, infectious diseases; R/O, rule out; ±, with or without.

November 2001, before systematic use of the algorithm, calls to the CDC regarding suspected smallpox cases resulted in 8 instances of variola virus testing (the results of which were all negative). In 2002, one case of great concern to state health officials was tested for smallpox virus after VZV results were determined to be negative [8]. During the response, the treating facility was closed. Concern arose because the rash started on the face, because it evolved slowly, and because lesions were in the same stage of development. The final diagnosis was HSV-2 infection [8–9]. As physicians and public health officials became more familiar with the algorithm, fewer requests for smallpox virus testing were received, and no other smallpox diagnostics were conducted (at the CDC) for calls in which the CDC was consulted. By 2004, most callers to the CDC were familiar with the algorithm.

The algorithm worked well to guide the clinical and public health response to cases in which smallpox was in the differential diagnosis. Telephone consultations provided reassurance in treating these patients and averted unnecessary and costly measures and the perceived need for variola virus testing. We found that the algorithm reinforced appropriate use of contact and isolation precautions and involvement of infection-control personnel.

Varicella was the most commonly diagnosed disease that was confused with smallpox, as was true during and after the smallpox eradication era. In outbreaks of variola major in England and Wales during 1946–1948, varicella accounted for 42% of suspected variola major cases that were not found to be smallpox [10]. In rash illness surveillance for suspected smallpox cases following country-wide or global eradication, varicella accounted for 37% of cases reported in the United States during 1970–1972, 69% of cases of suspected variola minor in Somalia during 1977–1979, and, after exclusion of erroneous or vague reports, 61% of cases reported globally to the World Health Organization during 1980–1988 [11–14]. We caution providers to remember the potential severity of varicella and other conditions that may be confused with smallpox. Two persons classified as having a low risk of smallpox died of varicella infection.

Other diagnoses in these studies of suspected smallpox cases were similar to those we included on the algorithm, including erythema multiforme, drug reactions, acne, insect bites, allergic
Department of health. The priority of the laboratory network is the development of the LRN, which was founded in 1999 as the national network of 100 testing laboratories at local, state, and federal levels, along with hospital-based, veterinary, agricultural, food, and environmental laboratories, to respond to biological and chemical terrorism and other public health emergencies. Requests for LRN testing are coordinated by each state’s department of health. The priority of the laboratory network is to expand the capacity to diagnose likely causes of disease and thereby rapidly rule out bioterrorist attack. By November 2002, all LRN laboratories had the capacity to conduct rapid assessments for VZV, by DFA or PCR, and 74 laboratories had the capacity to test generically for orthopoxvirus by PCR. Among Department of Health and Human Services–associated laboratories, PCR capacity specifically for variola virus can be conducted at 23 LRN laboratories and the CDC. Additional test capacity is available at select Department of Defense facilities.

As highlighted by the false-alarm case of smallpox from Ohio, additional diagnostic capacity at the state level (e.g., for HSV) would also be beneficial [8]. Specimens that test positive for VZV, HSV, or other pathogens do not need further testing. Unless epidemiological presentations indicate high likelihood of smallpox, testing for variola virus is contraindicated because of the high risk of a false-positive result. For other suspected orthopoxvirus infections, generic orthopoxvirus and/or vaccinia PCR testing is indicated.

The following limitations should be considered. First, early cases of classic smallpox in patients who seek medical care before the rash becomes vesicular or pusular will be missed. We consider this risk acceptable in the posteradication era, given the nonspecificity of earlier presentations of smallpox and the chaos that may ensue if earlier suspected cases are evaluated with laboratory testing for smallpox. If a smallpox case were confirmed, surveillance for smallpox would be expanded from probable cases (those meeting the clinical case definition and now classified as high risk by the algorithm) to suspected cases (any febrile rash illness with fever preceding development of rash by 1–4 days) to capture earlier presentations of disease [23]. However, whether observed in the hospital or discharged with close follow-up, these initially missed patients would clearly be classifiable within a few days as their rash evolved. Exposure to others before diagnosis would be limited by severity of the disease. Persons exposed to the patient during early stages of communicability, especially household members, may still respond to postexposure prophylaxis with smallpox vaccine. Second, the algorithm is not designed to detect the most severe

<table>
<thead>
<tr>
<th>Age group</th>
<th>No. of subjects</th>
<th>Moderate-risk cases (n = 8)</th>
<th>Low-risk cases (n = 35)</th>
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</thead>
<tbody>
<tr>
<td>Children and adolescents</td>
<td>11</td>
<td>Erythema multiforme (1), eczema (1)</td>
<td>Varicella (4), Gianotti-Crosti syndrome (2), herpes simplex virus type 1 infection (1), Stevens-Johnson syndrome (1), molluscum contagiosum (1)</td>
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<td>(age, &lt;18 years)</td>
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<td>Varicella (14), drug reaction (2), insect bites (2), disseminated herpetic zoster infection (1), disseminated herpes simplex type 2 infection (1), streptococcal infection (1), Behcet disease (1), Crohn disease (1), contact dermatitis (1), atypical cutaneous syndrome (1), allergic reaction (1)</td>
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<tr>
<td>Adults (age, ≥18 years)</td>
<td>32</td>
<td>Varicella (6), drug reaction (1)</td>
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and atypical forms of smallpox—that is, flat-type and hemorrhagic type. However, these cases were rare, comprising just 6.7% and 2.4%, respectively, of smallpox cases in hospitalized patients among unvaccinated persons in the study from India by Rao [1]. The frequency of these types in the community would have been considerably lower. In addition, infection-control measures are indicated for all potentially infectious conditions, regardless of etiology, which would also limit spread of variant presentations of smallpox. Third, the algorithm may miss many cases of variola minor and modified variola major that present in a less severe form and are more likely than classic smallpox (variola major) to mimic varicella than classic smallpox [1, 2]. In the study by Rao [1], 2% of smallpox cases in unvaccinated persons had a modified presentation, and 25% of cases in vaccinated persons had a modified presentation. Currently, ~58% of the US population has received smallpox vaccination, but, for the majority of these individuals, that history is so remote that smallpox is likely to present classically in all but a small minority of recent vaccinees.

Medical preparedness for a bioterror event in the United States has been improved by development and successful use of a simple clinical algorithm that guides the classification and appropriate clinical and public health follow-up for persons with acute febrile vesicular pustular rash illnesses that raise suspicions for smallpox. This algorithm is currently being evaluated for clarity and specificity in a multiple-center study, results of which may suggest further refinements. We recommend continued use of the algorithm in the United States and elsewhere.

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