Acute, Generalized Vesicular or Pustular Rash Illness Testing Protocol in the United States

Introduction
This protocol has been developed to illustrate the types of laboratory testing to be undertaken in different situations involving patients with acute, generalized vesicular or pustular rash illness. The protocol is composed of four charts, each illustrating a different set of symptoms or circumstances. It has been designed to correlate with “Evaluating Patients for Smallpox: Acute, Generalized Vesicular or Pustular Rash Illness Protocol” (www.bt.cdc.gov/agent/smallpox/diagnosis/riskalgorithm). This is a pre-event algorithm, designed to address testing needs when no poxvirus emergency has been detected or declared. Changes to this algorithm may be required in an event. Any updates to the algorithm will be announced by the Laboratory Response Network.

Chart 1 lists the symptoms associated with acute, generalized vesicular or pustular rash illness and categorizes the risk of smallpox according to the patient’s signs and symptoms.

Chart 2 presents a flow chart for laboratory testing of specimens from patients presenting with acute, generalized vesicular or pustular rash illness, following the assessment per the “Acute, Generalized Vesicular or Pustular Rash Illness” protocol (see above and chart 1 for abstraction of the protocol). A two-armed algorithm is presented to reduce the time to receive results and to ensure that testing of high-risk specimens is confined to laboratories with appropriate biosafety levels and expertise. The two arms of the testing algorithm are for 1) specimens from individuals with low- and moderate-risk symptoms and 2) specimens from individuals with high-risk symptoms.

Major points:
   a) high-risk specimens/cases require consultation with CDC
   b) low- or moderate-risk specimens/cases should be worked-up for more common causes of febrile exanthema. Due to the differences in run temperature between the Non-variola Orthopoxvirus PCR and the Orthopoxvirus PCR, the two assays cannot be performed simultaneously. If orthopoxvirus is suspected, then the Non-variola Orthopoxvirus PCR permits the laboratory to identify an orthopoxvirus and reassure that the specimen does not contain variola. The Orthopoxvirus generic PCR can be performed subsequently to provide additional confidence in the result.
   c) in the absence of endemic smallpox disease, the indiscriminate use of variola tests will lead to false positives.

Chart 3 presents a testing algorithm that should be used when a smallpox vaccine adverse event or monkeypox infection is suspected.

Chart 4 presents an orthopoxvirus testing algorithm for environmental samples.

The testing protocols are supported at Laboratory Response Network (LRN) reference laboratories. Details for performance and interpretation of each assay are specified in each LRN procedure.

Details on specimen collection can be found at the following websites:

Smallpox vaccine:  www.bt.cdc.gov/agent/smallpox/vaccination/vaccinia-specimen-collection.asp
Monkeypox:  www.cdc.gov/ncidod/monkeypox/diagspecimens.htm
ACUTE, GENERALIZED VESICULAR OR PUSTULAR RASH ILLNESS PROTOCOL

Patient with Acute, Generalized Vesicular or Pustular Rash Illness

Institute Airborne & Contact Precautions
Alert Infection Control on Admission

Low Risk of Smallpox
(see criteria below)

Moderate Risk of Smallpox
(see criteria below)

High Risk of Smallpox
(see criteria below)

Patient

Low Risk of Smallpox
(see criteria below)

History and Exam
Highly Suggestive of Varicella

Varicella Testing
Optional

Test for VZV and Other Conditions as Indicated

Diagnosis Uncertain

ID and/or Derm Consultation
VZV +/- Other Lab Testing as Indicated

Non-Smallpox Diagnosis Confirmed
Report Results to Infx Control

No Diagnosis Made
Ensure Adequacy of Specimen
ID or Derm Consultant Re-evaluate Patient

Cannot R/O Smallpox
Contact Local/State Health Dept.

Appropriate Treatment for Varicella/Other Conditions as Clinically Indicated

Response Team Advises on Management and Specimen Collection

Testing at CDC

NOT Smallpox
Continue Diagnostic Testing

SMALLPOX

Risk of Smallpox

High Risk of Smallpox
1. Febrile prodrome AND
2. Classic smallpox lesion AND
3. Lesions in the same stage of development

Moderate Risk of Smallpox
Febrile prodrome AND one other MAJOR smallpox criterion OR
Febrile prodrome AND >4 MINOR smallpox criteria

Low Risk of Smallpox
No febrile prodrome OR
Febrile prodrome AND <4 MINOR smallpox criteria

Major Smallpox Criteria:
• Febrile prodrome
  – >101F, 1-4 days prior to rash onset
  – with headache, back ache, or abdominal pain
• Firm, deep-seated, well-circumscribed vesicles/pustules
• Lesions in the same stage of development in any one area of the body

Minor Smallpox Criteria:
• Centrifugal distribution of lesions
• First lesions in the pharynx, oral mucosa
• Patient appears “toxic”
• Slow evolution of rash
  – 1-2 days each stage: macule, papule, vesicle
• Lesions on the palms and soles

Chart 1

11/14/2007
**LABORATORY TESTING FOR ACUTE, GENERALIZED VESICULAR OR PUSTULAR RASH ILLNESS IN THE UNITED STATES**

**Low and Moderate Risk Specimens**
(Green and Yellow Boxes)
- Sentinel Laboratories and/or LRN Reference Laboratories
- Use BSL-2 facilities
  - DFA: VZV and HSV
  - PCR: VZV, HSV, Enterovirus (where available)
  - EM: (where available)
  - Viral culture: as appropriate
- Consider biopsy for erythema multiforme

**High-Risk Specimens**
(Red Box)
- Immediately refer to Variola Testing Laboratory
  - Initiate Chain-of-Custody documentation at FBI direction

**Consultation with PHL and CDC**
- Rule out variola, prior to other testing, at laboratory with specific variola test capacity. LRN-designated Variola Testing Laboratories and CDC will have this capacity. CDC will test split sample simultaneously.
- Results must not be released without CDC confirmation.
- Once reliable performance of assays in surge labs is demonstrated (post-event) CDC confirmation may be discontinued.

**Variola Testing Laboratories**
- Enhanced BSL-3 required
  - Variola PCR
  - Orthopoxvirus PCR
  - Non-variola orthopoxvirus PCR
  - EM (if available)

**Non-variola orthopoxvirus PCR POS**
- Vaccine-related adverse event or possible monkeypox.
  - Contact CDC Poxvirus Helpdesk 404-639-4129
- For verification of the result, the Orthopoxvirus PCR may be used

**Non-variola orthopoxvirus PCR NEG**
- No further testing (unless clinically indicated)

**All orthopox tests NEG:**
- Perform the following:
  - DFA: VZV, HSV
  - PCR: VZV, HSV, Enterovirus
  - Viral culture and other diagnostic tests as clinically indicated.

**If all tests are NEG:**
- Re-evaluate patient condition and assess need for dermatologic and histologic testing, including tests for erythema multiforme; consider biopsy.
- For additional confirmation that orthopoxvirus is not present in the specimen, the Orthopoxvirus PCR may be used.

**If patient symptoms progress to more closely resemble smallpox, refer all specimens to CDC and/or LRN labs with Variola PCR testing capability. Sequester all viral cultures and specimens. Contact PHL for transport of specimens.**

**Take digital photos of clinical presentations for electronic consultations.**

**EM at local facility**
- BSL-3 preparation of grids
- Non-variola orthopoxvirus PCR:
  - POS:
  - Vaccine-related adverse event or possible monkeypox.
  - Contact CDC Poxvirus Helpdesk 404-639-4129
  - For verification of the result, the Orthopoxvirus PCR may be used
- Evaluated by Healthcare Practitioner, Infectious Disease or Dermatology Specialist

**Low and Moderate Risk Specimens**
- Sentinel Laboratories and/or LRN Reference Laboratories
- DFA: VZV and HSV
- PCR: VZV, HSV, Enterovirus (where available)
- EM: (where available)
- Viral culture: as appropriate
- Consider biopsy for erythema multiforme

**Variola Testing Laboratories Enhanced BSL-3 required**
- Variola PCR
- Orthopoxvirus PCR
- Non-variola orthopoxvirus PCR
- EM (if available)

**Variola & Orthopox PCR both POSITIVE**
- HIGHLY suggestive of SMALLPOX
- CALL CDC immediately prior to release of results
- Director’s Emergency Operations Center (DEOC) 770-488-7100
Acceptable specimens:
- Vesicular “touch prep”
- Vesicle roof
- Vesicular swab
- Ocular swab or impression slide
- Biopsy specimens

Take digital photos of clinical presentations for electronic consultations.

**Patient with Suspected Vaccine-Related Adverse Event or Monkeypox**

All Sentinel Laboratory and Reference LRN with no Orthopoxvirus PCR capacity

Refer only

LRN Labs (with PCR capability)
- Non-variola Orthopoxvirus PCR
- Orthopoxvirus PCR
- EM – (if available)

Note: A non-variola orthopoxvirus PCR POS and orthopoxvirus PCR NEG should not be generated. If that occurs, consult CDC Poxvirus Helpdesk 404-639-4129

Test Results

Non-variola orthopoxvirus PCR: POS
Orthopoxvirus PCR: POS
EM (optional): POS for poxvirus

Vaccine-related adverse event or monkeypox.
Evaluate exposure history and contact CDC to submit specimen for confirmatory tests.
Contact CDC Poxvirus Helpdesk 404-639-4129

Non-variola orthopoxvirus PCR: NEG
Orthopoxvirus PCR: NEG
EM (optional): NEG for poxvirus

- Re-evaluate patient condition and assess need for dermatologic and histologic testing, including tests for erythema multiforme; consider biopsy.
- Perform:
  - DFA: VZV, HSV
  - PCR: VZV, HSV, Enterovirus
  - Viral culture and other diagnostic tests as clinically indicated

Non-variola orthopoxvirus PCR: NEG
Orthopoxvirus PCR: POS
EM: POS or NEG for poxvirus

Orthopoxvirus identified - possible variola*
Refer immediately to CDC for confirmatory testing
Call the Director's Emergency Operation Center (DEOC) 770-488-7100

** includes any non-variola orthopoxvirus, such as vaccinia, monkeypox and cowpox.

*Note: Could also represent differential sensitivities of the assays
LABORATORY TESTING FOR ENVIRONMENTAL SAMPLES IN THE UNITED STATES

Environmental Samples
Law Enforcement Credible Threat Assessment
(Explosives, radiation, hazardous chemicals and toxins ruled out)

Sentinel Laboratory
Refer only

LRN Reference Laboratory
• Orthopoxvirus PCR
• Non-variola orthopoxvirus PCR
• EM – (with CDC consultation only)

Test Results

Note: A non-variola orthopoxvirus PCR POS and orthopoxvirus PCR NEG should not be generated. If that occurs, contact CDC Poxvirus Helpdesk.  404-639-4129

Orthopoxvirus PCR: POS
Non-variola orthopoxvirus PCR: NEG
EM: POS or NEG for poxvirus

Orthopoxvirus material identified - most likely non-variola
Refer to CDC for confirmatory testing.
Contact CDC Poxvirus Helpdesk 404-639-4129

Orthopoxvirus ruled out.
Assess need for further testing with law enforcement. Report negative results to other groups investigating specimens.

Orthopoxvirus material identified - possible variola.
Refer immediately to CDC for confirmatory testing.
Call the Director’s Emergency Operation Center (DEOC) 770-488-7100

Orthopoxvirus PCR: NEG
Non-variola orthopoxvirus PCR: NEG
EM: NEG for poxvirus

Orthopoxvirus PCR: NEG
Non-variola orthopoxvirus PCR: POS
EM: POS or NEG for poxvirus