Recognizing and Diagnosing Febrile Rash Illnesses

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Division of High Consequence Pathogens and Pathology

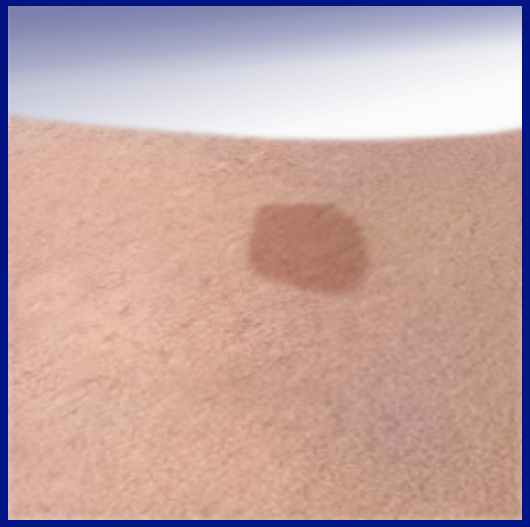
Disclosures

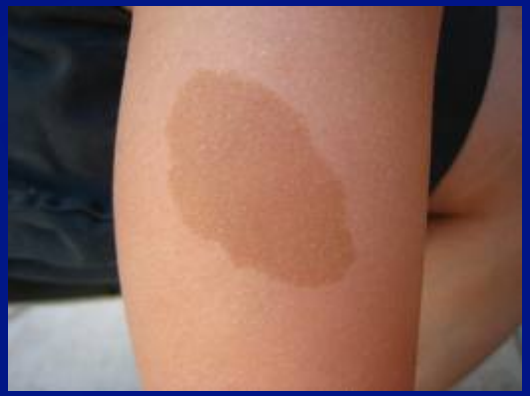
- **Disclosure of Relevant Financial Relationships**
  - I have no financial relationships to disclose.

Dermatology 101
Flat Lesions

- **Macule**
  - < 5mm
  - Circumscribed color change
  - Flat, not raised / not palpable

- **Patch**
  - > 5mm
  - Circumscribed color change
  - Flat, not raised / not palpable

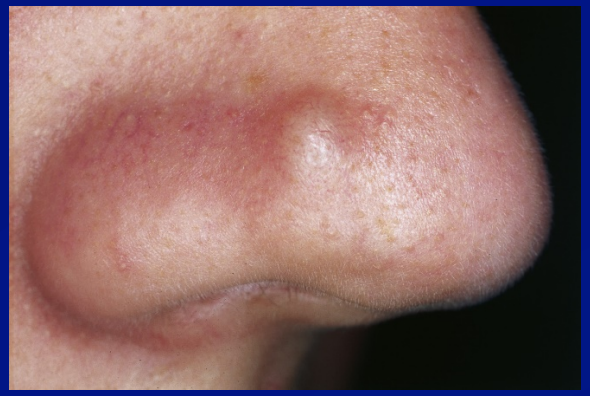


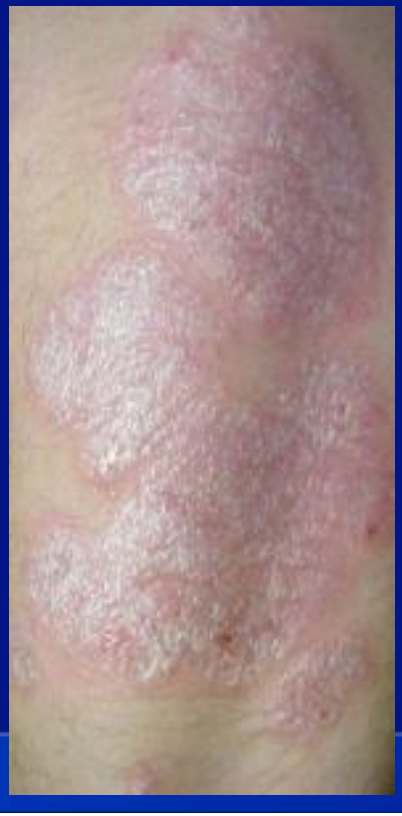


https://step2.medbullets.com/dermatology/120040/terminology-of-skin-lesions

Dermatology 101
Raised Lesions

- **Papule**
  - < 5mm
  - Solid, raised lesion / palpable
- **Plaque**
  - > 5mm
  - Solid, raised lesion / palpable

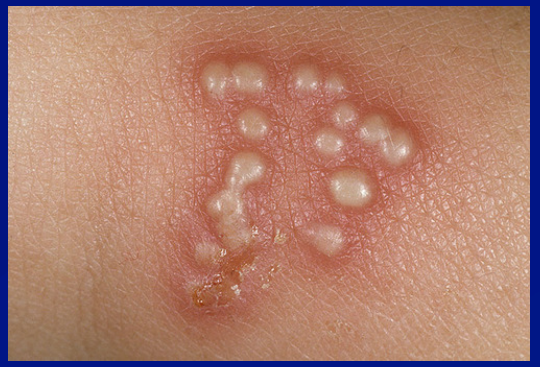


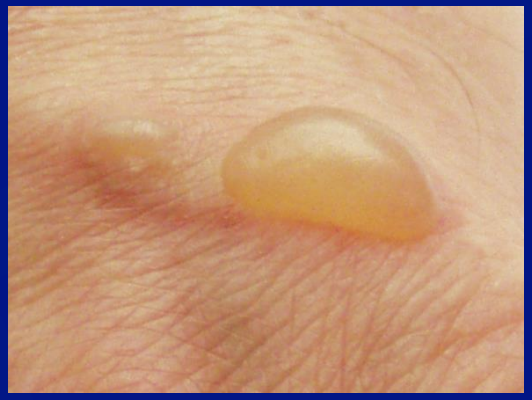


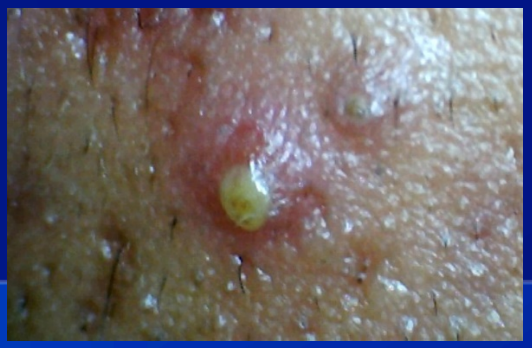
https://step2.medbullets.com/dermatology/120040/terminology-of-skin-lesions

Dermatology 101
Fluid-Filled Lesions

- **Vesicle**
  - < 5mm
  - Raised, clear, fluid-filled
- **Bulla**
  - > 5mm
  - Raised, clear, fluid-filled
- **Pustule**
  - Circumscribed cavity of skin containing pus



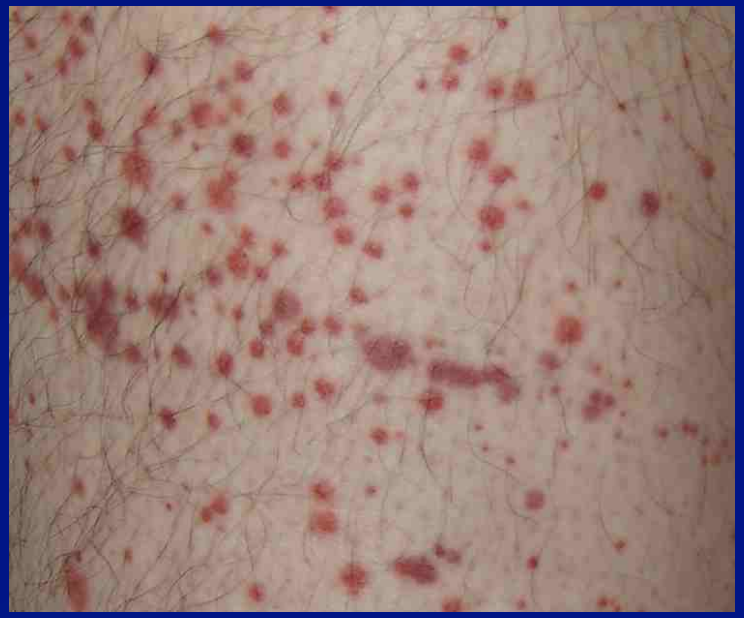


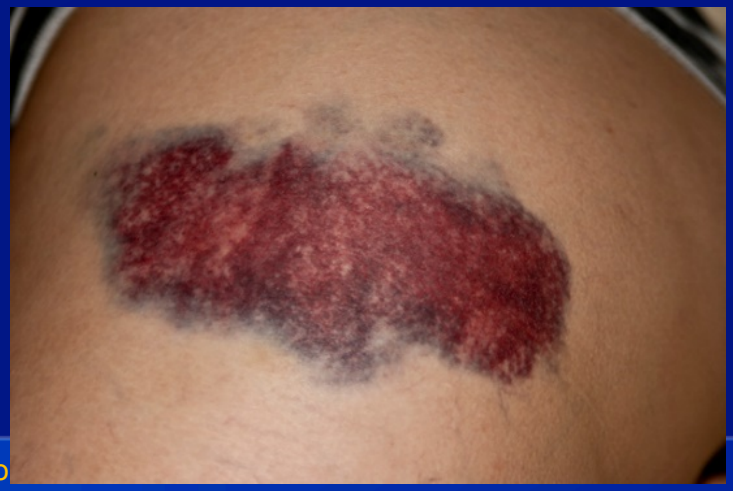


https://step2.medbullets.com/dermatology/120040/terminology-of-skin-lesions

Dermatology 101
Nonblanching Lesions

- **Petechiae**
  - Pinpoint red, brown, or purple macules
  - Capillary bleeding
- **Purpura**
  - 4-10mm red, brown, or purple macules
  - Blood extravasation into tissue



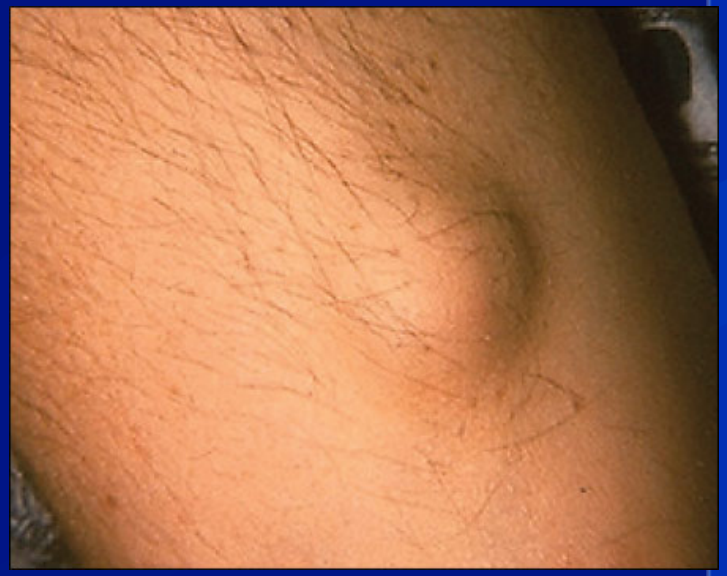


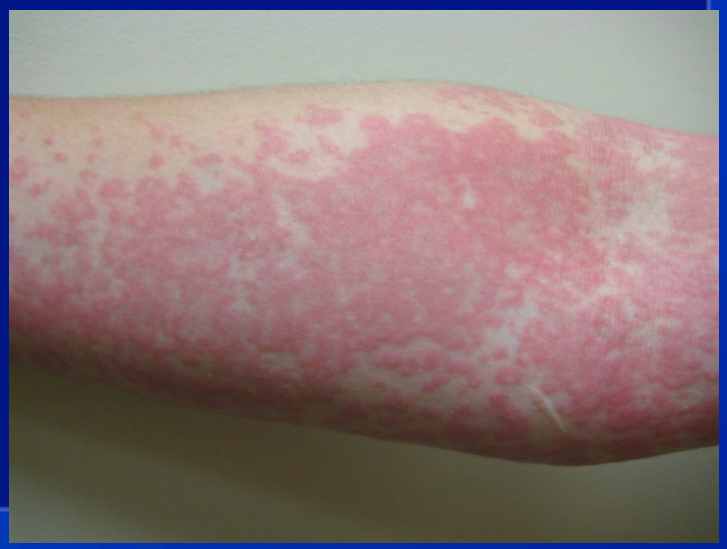
https://step2.medbullets.com/dermatology/120040/terminology-of-skin-lesio

Dermatology 101
Other Lesions

- **Nodule**
  - Circumscribed solid proliferation
  - Apart from surrounding tissue
  - Often occurring in the dermis or subcutis

- **Wheal (hive)**
  - Pale red papule or plaque
  - Palpable and pruritic
  - Caused by edema in the upper dermis

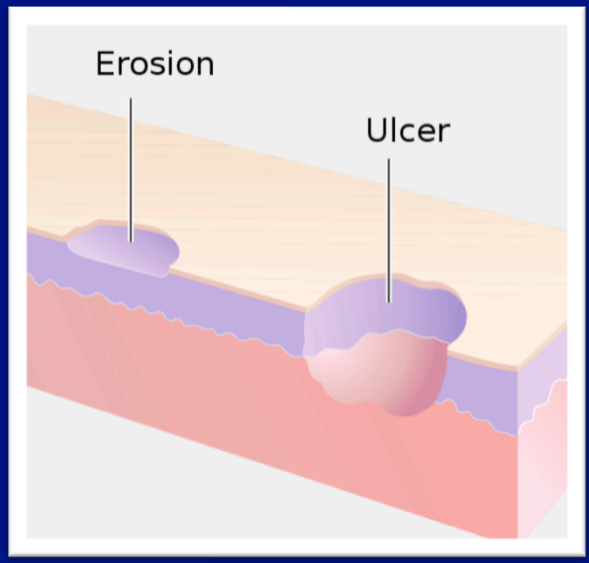


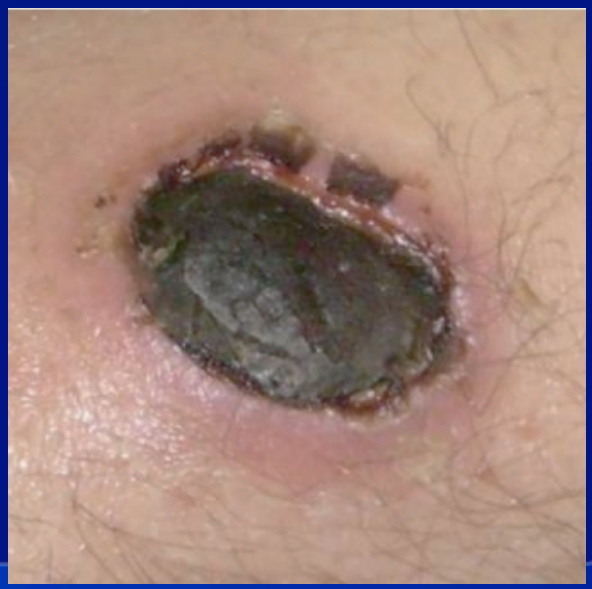


https://step2.medbullets.com/dermatology/120040/terminology-of-skin-lesions

Dermatology 101
Other Lesions

- **Erosion**
  - Defect of the epidermis not affecting the dermis
- **Ulcer**
  - Skin defect extending into the dermis or deeper
- **Eschar**
  - Dark, dead, separated tissue (slough) found in a wound extending into the dermis or deeper



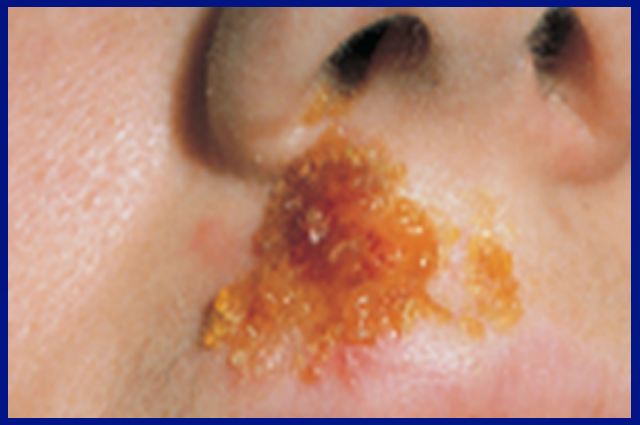


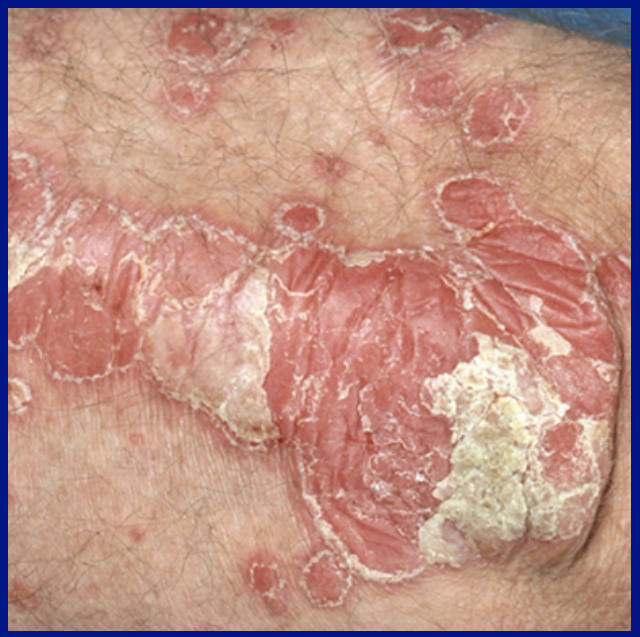
https://commons.wikimedia.org/wiki/File:Ulcers,_fissures,_and_erosions.svg

https://openi.nlm.nih.gov/detailedresult.php?img=PMC2225464_SRCM2007-81592.003&req=4

Dermatology 101
Other Lesions

- **Crust**
  - Rough surface consisting of dried, serum, blood, bacteria, and/or cellular debris
- **Scale**
  - Raised, red, dry flakes of stratum corneum





https://accessmedicine.mhmedical.com/content.aspx?bookid=392&sectionid=41138697

Dermatology 101
Other Terms

- **Exanthem**
  - Cutaneous eruption occurring as a symptom of a general disease
- **Enanthem**
  - An eruption involving the mucous membranes

Approach to the Patient with Fever and Rash
Key Questions / Considerations

- Characteristics of the lesions
- Distribution and progression of the rash
- Timing of the onset in relation to fever
- Change in morphology, such as papules to vesicles or petechiae
- Symptoms associated with the rash (e.g., pain, pruritus, numbness)

Adapted from https://www.uptodate.com/contents/fever-and-rash-in-the-immunocompetent-patient

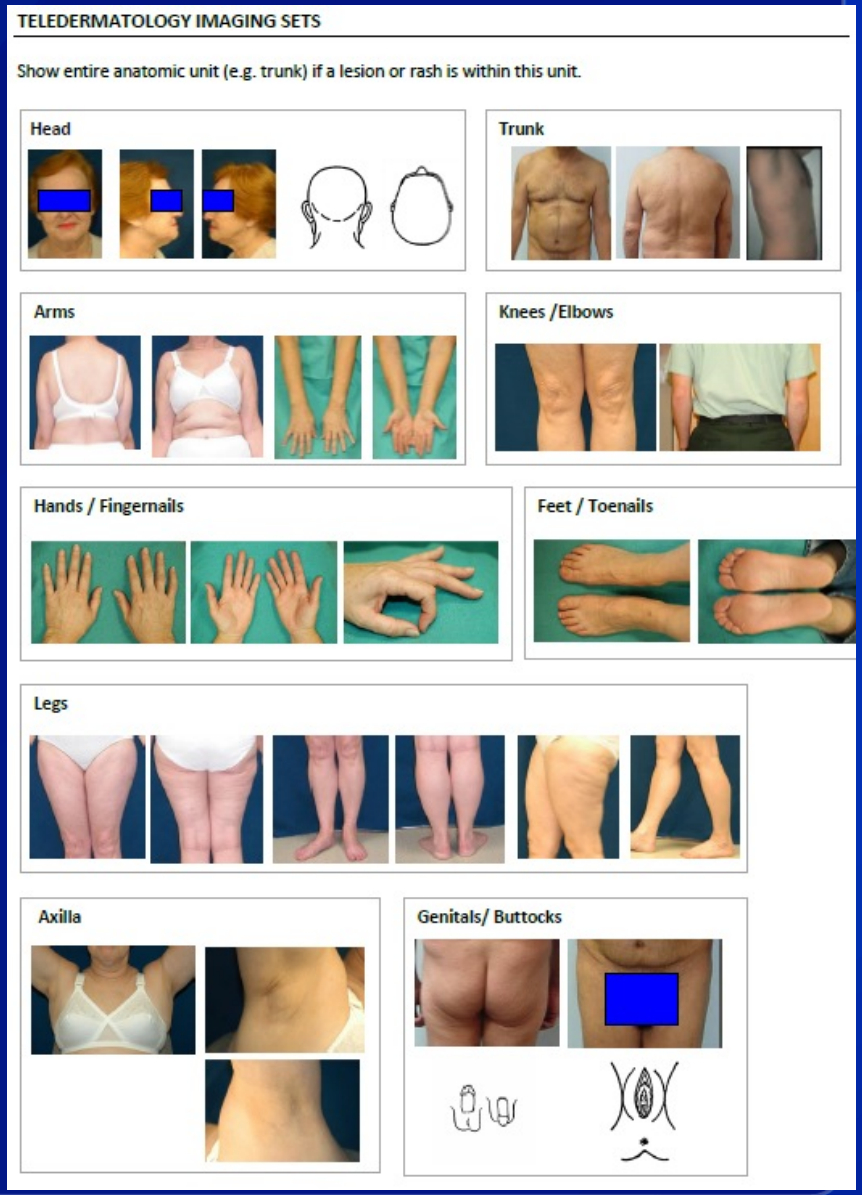
Approach to the Patient with Fever and Rash
Key Questions / Considerations

- Age of the patient
- Season of the year
- Travel history
- Geographic location
- Exposures, including to insects (especially ticks and mosquitoes), animals (both wild and domestic), and ill contacts
- Medications
- Immunizations and history of childhood illnesses
- Immune status of the host

Adapted from https://www.uptodate.com/contents/fever-and-rash-in-the-immunocompetent-patient

Teledermatology

- **Before and After Sending the Consult**
  - Review images for focus and adequate views before the patient leaves.
  - Send only helpful and clear images to the consultant.
  - Do not alter images in any way after taken.
  - Label images, transmitted text and consultant response to become part of a secure, retrievable medical record.
- **Camera**
  - Digital (avoid PDAs; use only high quality image capable cell phone if this is the only camera option available)
  - Ideal resolution of 1024 X 768 (about 0.8 Megapixels); minimum 800 X 600 pixels
  - Macro mode capability is ideal (“flower” image)



http://www.americantelemed.org/main/membership/ata-members/ata-sigs/teledermatology-sig

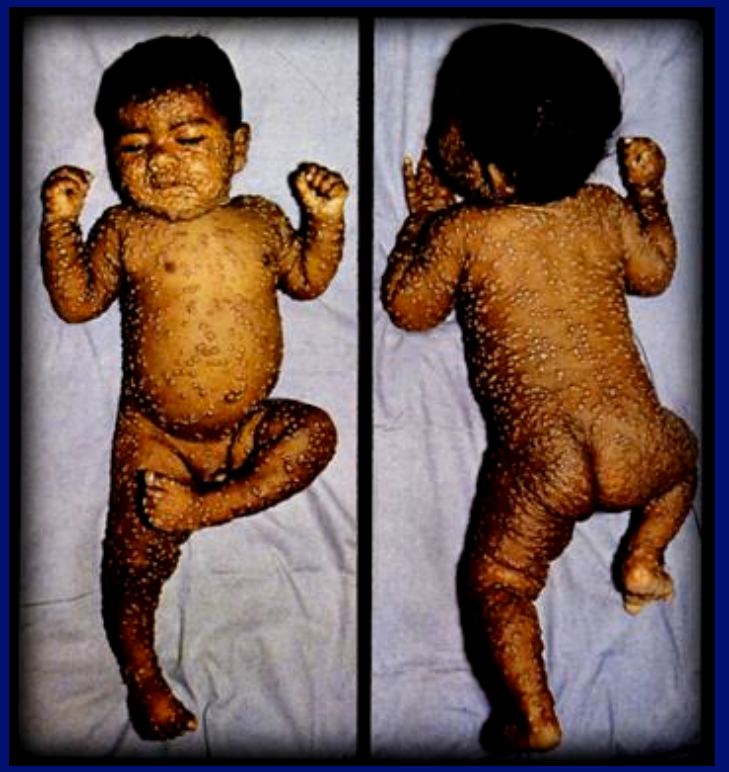
Teledermatology- Taking the Image

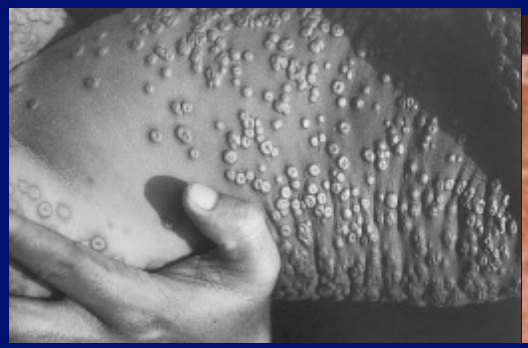
- **Background** - Use a solid, neutral color perpendicular to camera angle.
- **Lighting** - Diffuse, indirect light is best. Avoid shadows.
  - Indoors – fluorescent day-light or full spectrum bulbs are best (avoid incandescent).
  - Outdoors – use well-lit, but evenly shaded area if sunny.
- **Flash** - Helps to eliminate shadows. Test to see if needed. May cause white-out if too close.
- **Compression** - Use JPEG medium or low setting (no more than 20:1).
- **Focus** - Adjust camera and patient to have camera angle perpendicular to the skin lesions being imaged. Use auto-focus with area of interest in center of frame. If not possible, focus first on the area of interest, depress shutter button half-way to focus, then move the camera to center the image before fully depressing shutter button.
- **Views** - Take to show location and arrangement of lesions. Take several views
  - Far - entire body or obvious region
  - Medium - area involved central but include an anatomical landmark such as the navel or hand
  - Close-Up - if you have a macro capacity–the "flower" image, this can be taken under 18 inches from the skin – otherwise you may use the optical zoom, if present, to focus for a close-up. Use straight on and oblique views for close-ups.
- **Extra Tips** - Use a chaperone if needed; avoid distracting jewelry and clothing; in hairy areas tape or press back to show underlying skin changes. For face shots, eyes should be open. Use measurement tools as appropriate.

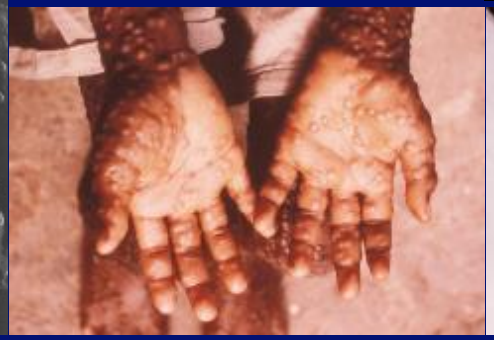
http://www.americantelemed.org/main/membership/ata-members/ata-sigs/teledermatology-sig

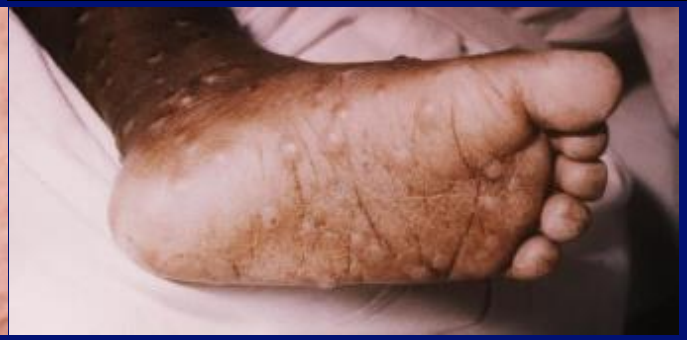
Smallpox

- Causative agent: *variola virus*
- Clinical presentation: disseminated vesicular/pustular rash associated with fever, prostration, and malaise
- Transmission: human-to-human via respiratory droplets and lesion exudates
- Animal reservoir: none

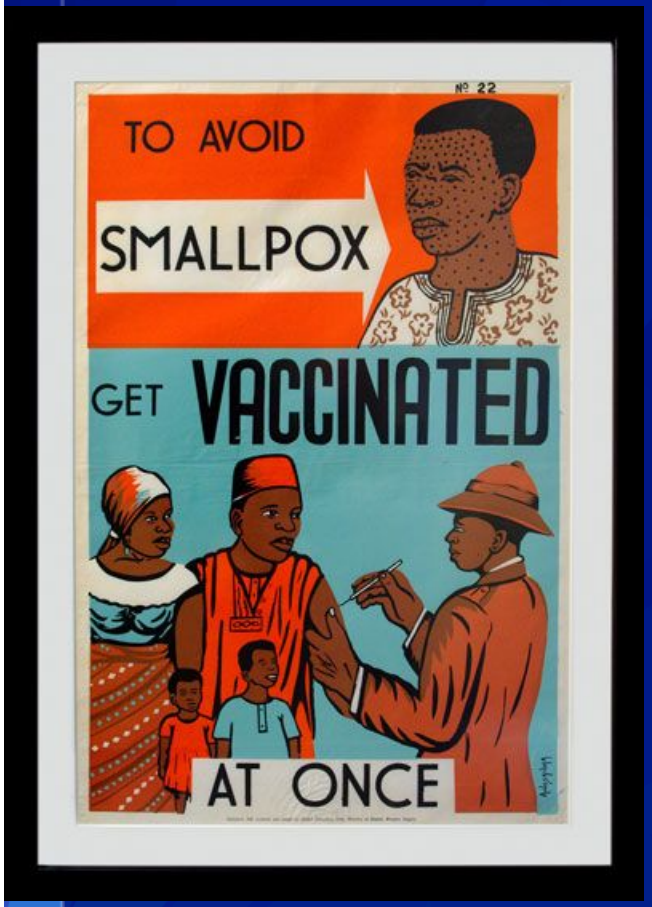


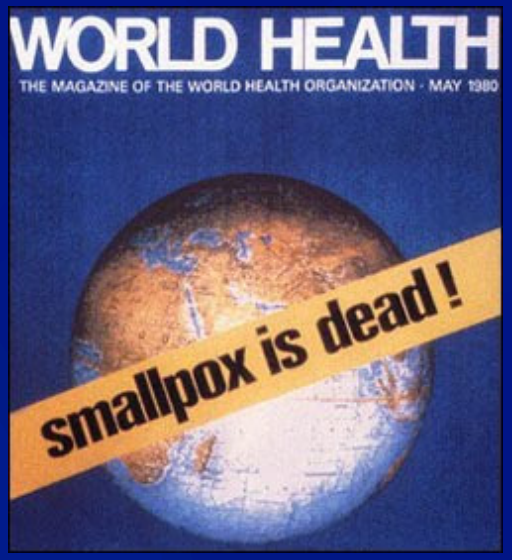


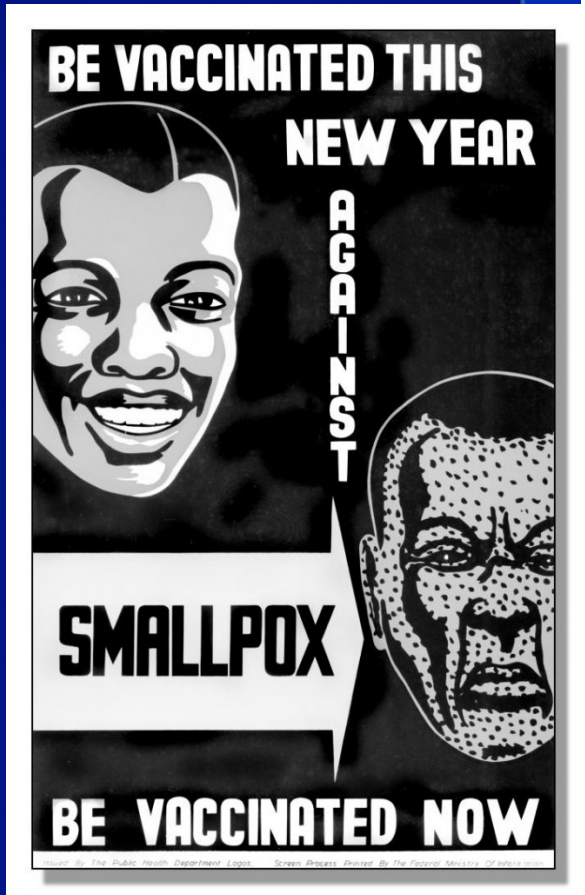




Smallpox Eradication







Smallpox as a Bioweapon

Building 600, where research was conducted

Fermentors in Building 221

FDA Variola Vials, 2014

CNN Health » CDC: Smallpox found in NIH storage room is alive

Live TV | U.S. Edition

CDC: Smallpox found in NIH storage room is alive

By Jen Christensen, CNN

Updated 3:07 PM ET, Fri July 11, 2014

http://www.cnn.com/2014/07/11/health/smallpox-found-nih-alive/index.html

Synthetic Biology

Science Home News Journals Topics Careers

How Canadian researchers reconstituted an extinct poxvirus for $100,000 using mail-order DNA

By Kai Kupferschmidt | Jul. 6, 2017 , 5:00 PM

SHARE

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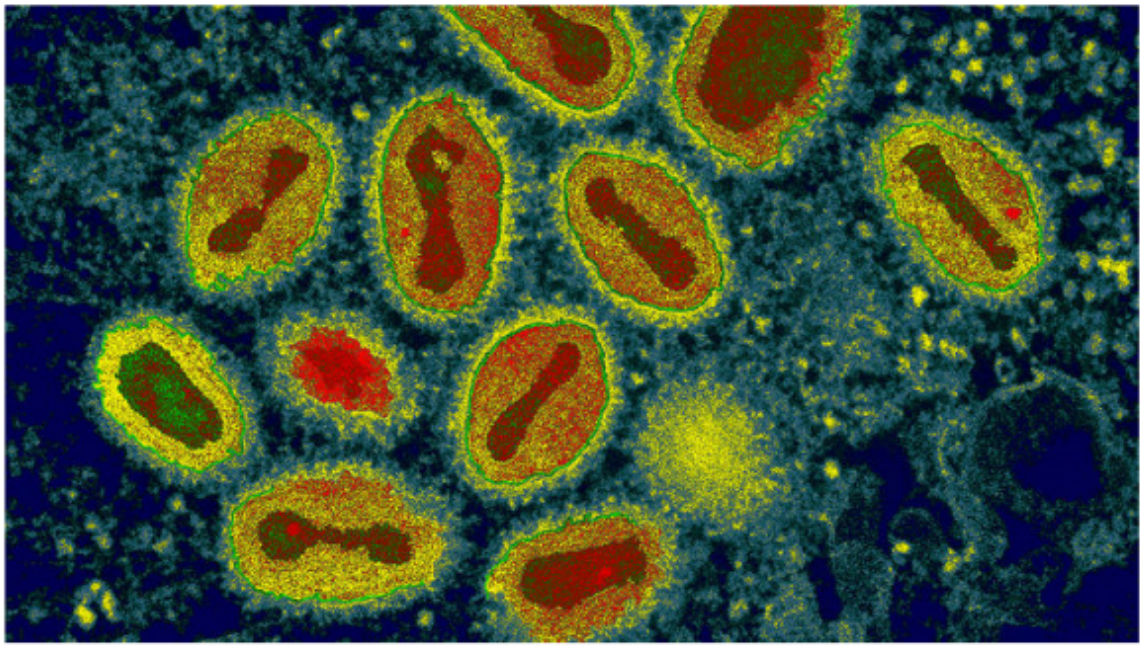
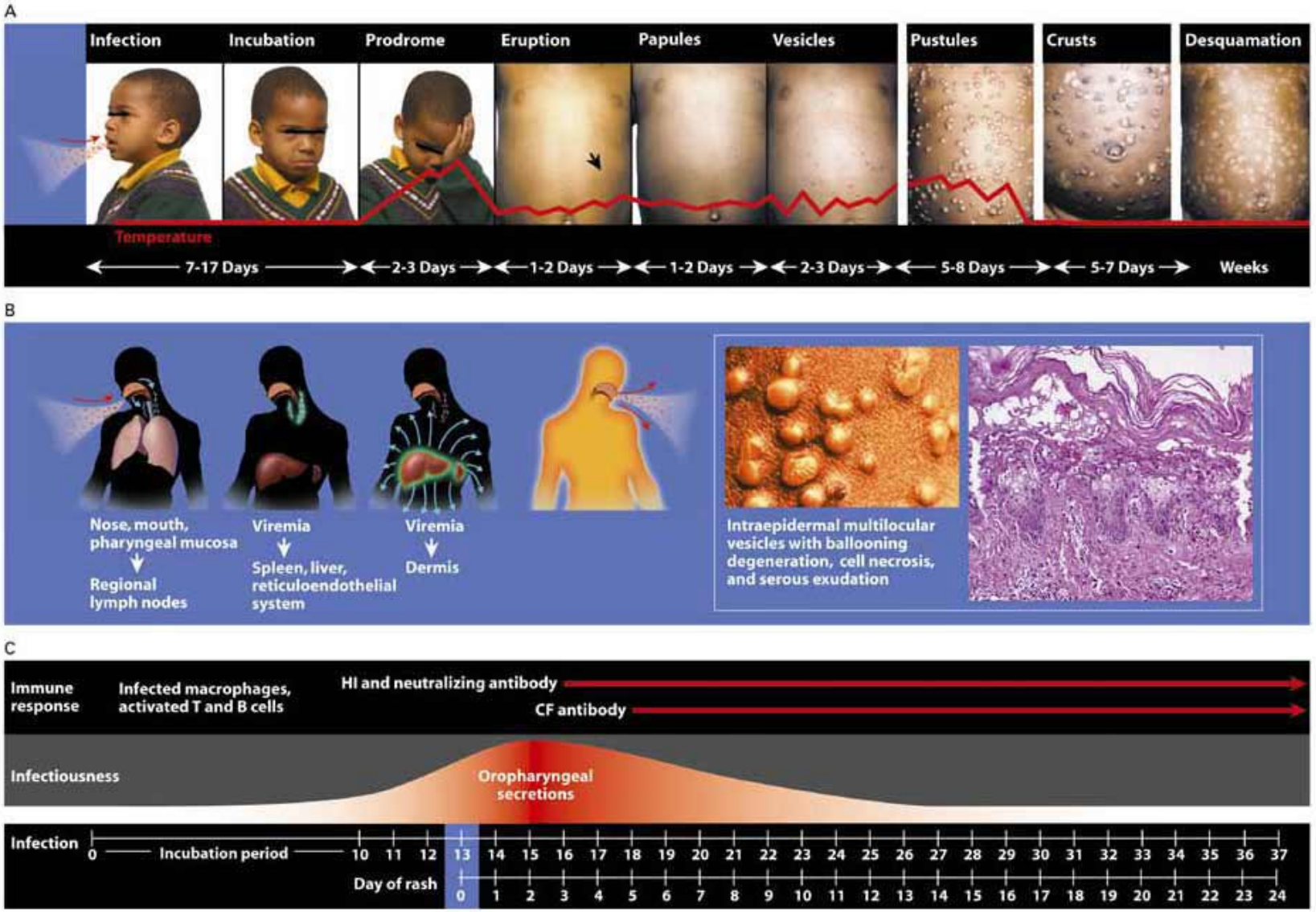


An unpublished study suggests that making variola, the virus that causes smallpox, is neither expensive nor difficult.

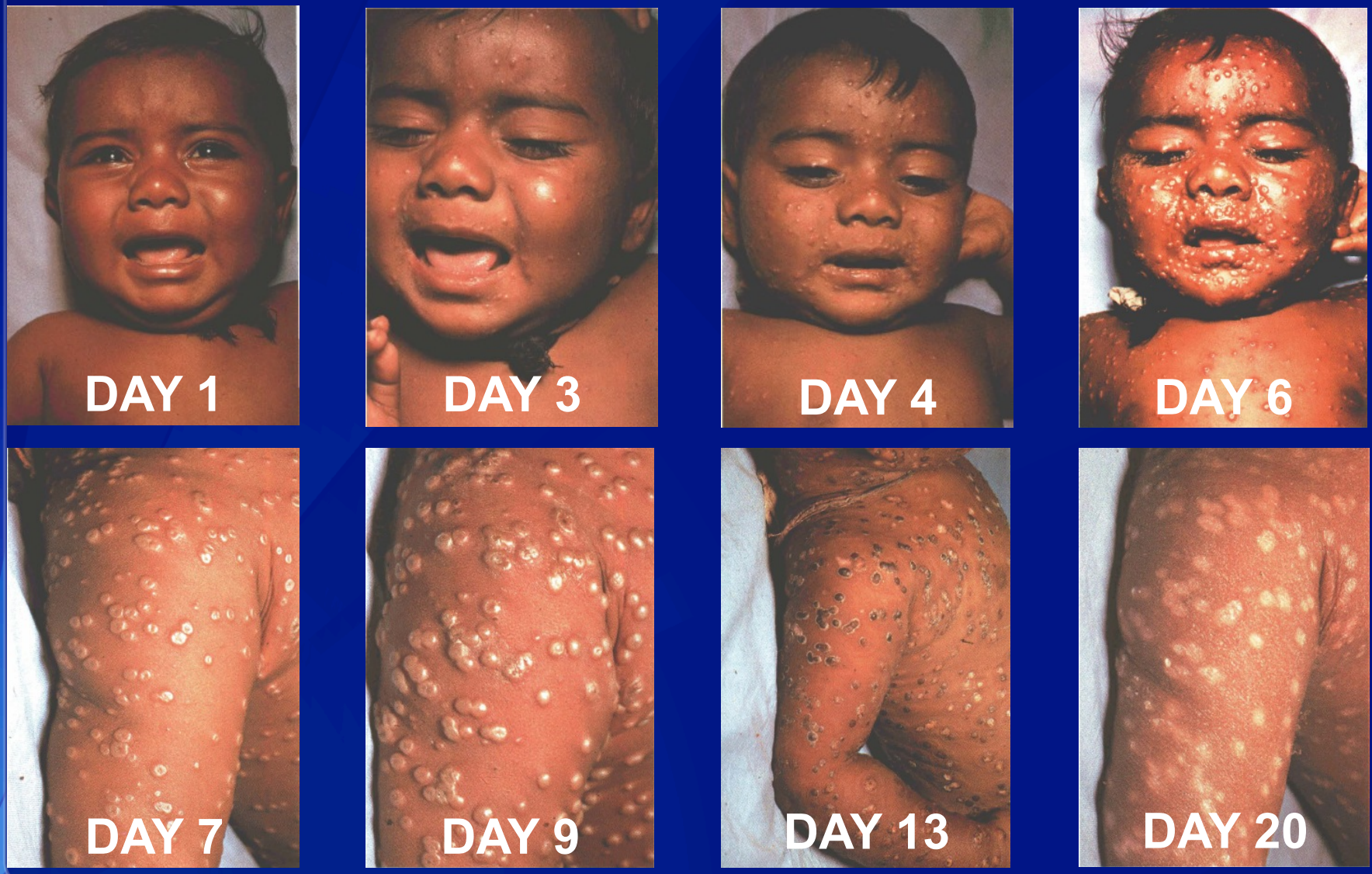
http://www.sciencemag.org/news/2017/07/how-canadian-researchers-reconstituted-extinct-poxvirus-100000-using-mail-order-dna

Smallpox Pathogenesis



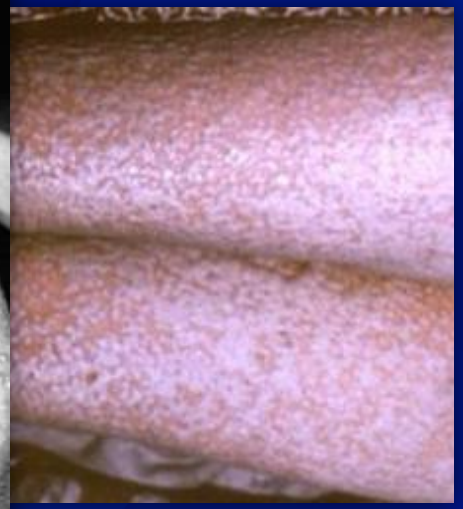
Diagnosis and management of smallpox. Breman JG, Henderson DA. N Engl J Med. 2002 Apr 25;346(17):1300-8.

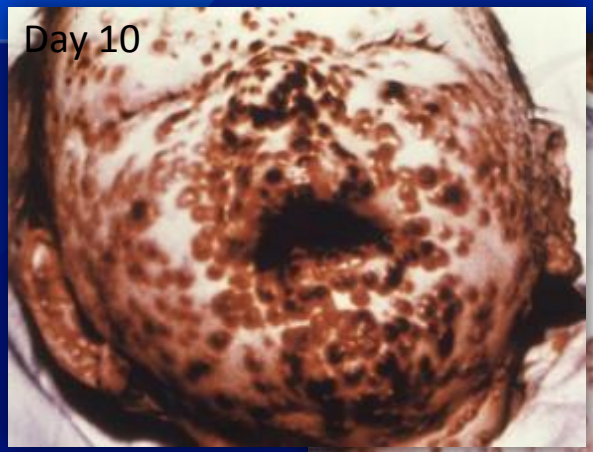
Rash progression

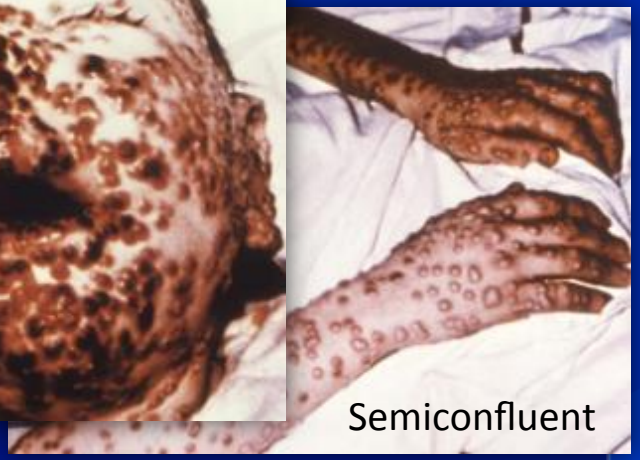


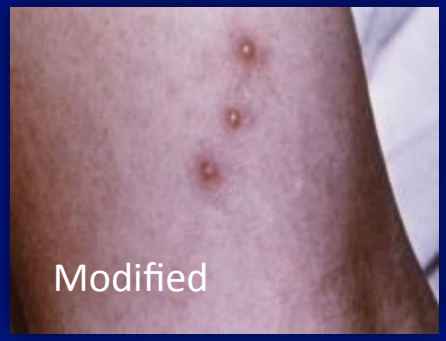
- Fenner, et al. Smallpox and its Eradication.

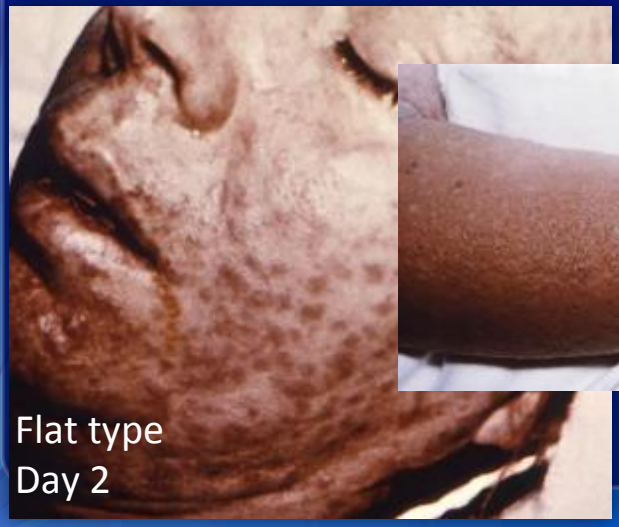
Variola Major Types

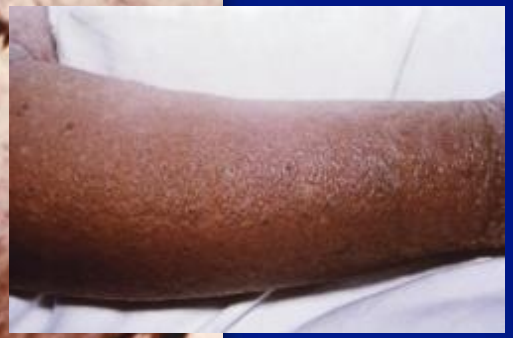


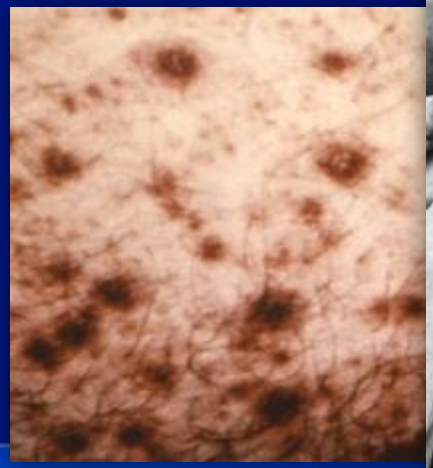


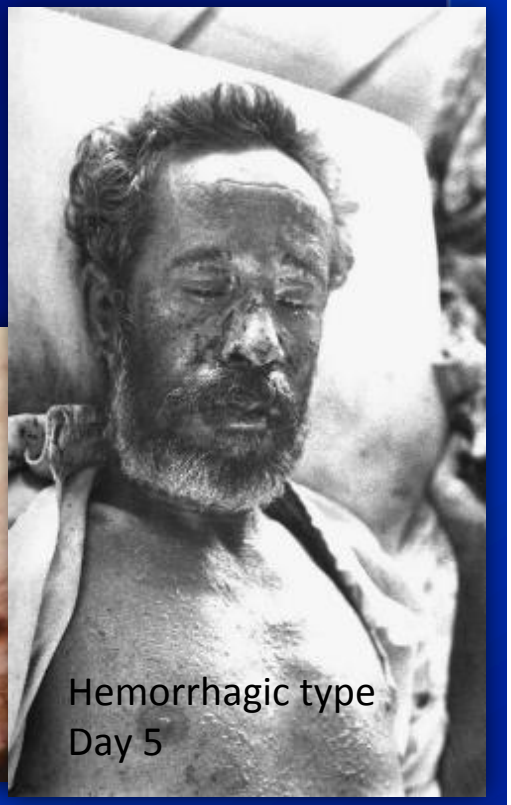




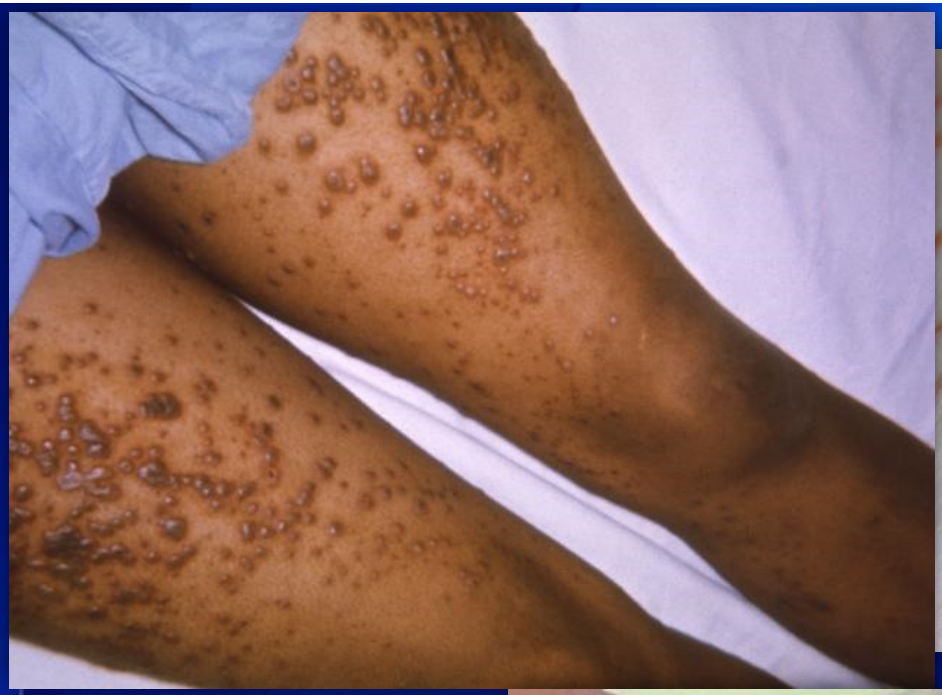


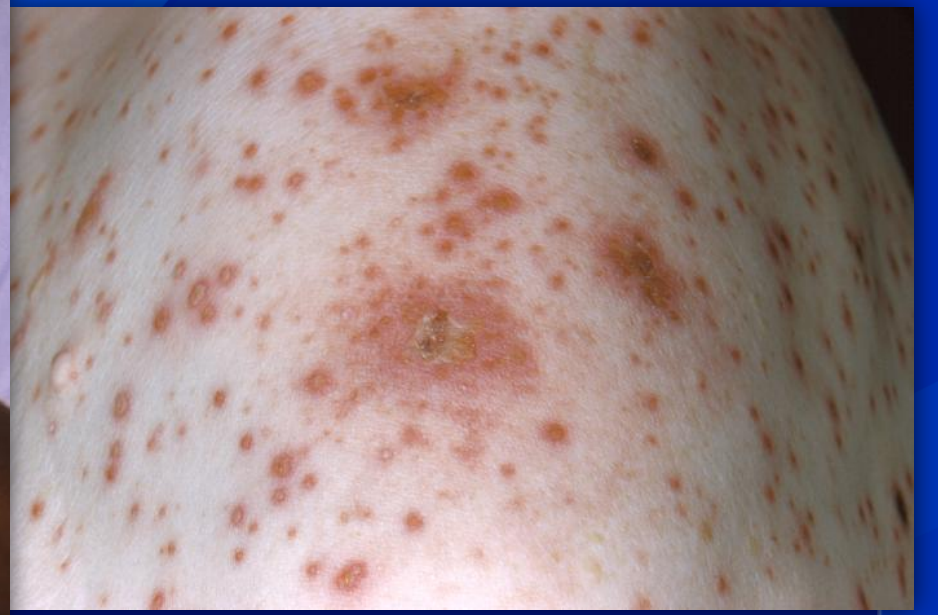


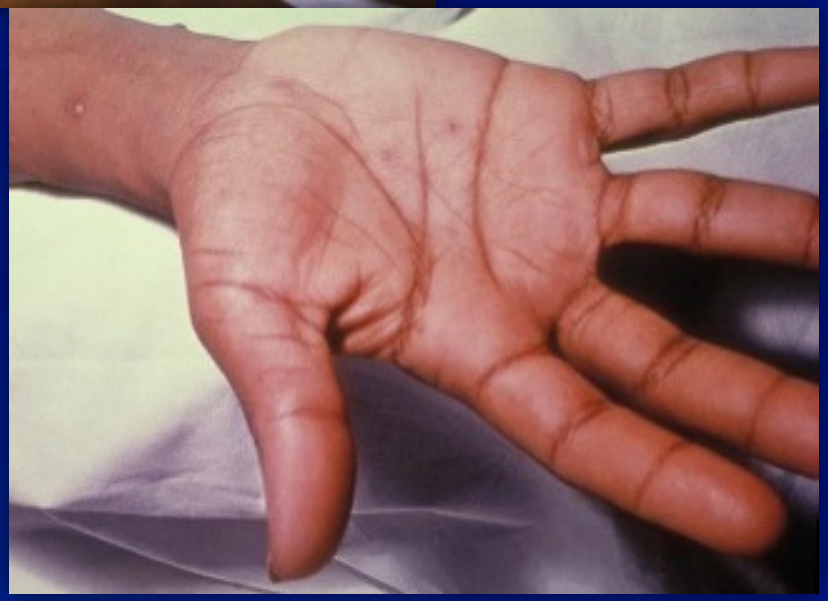




Smallpox Differential Diagnosis







Varicella-Zoster Virus

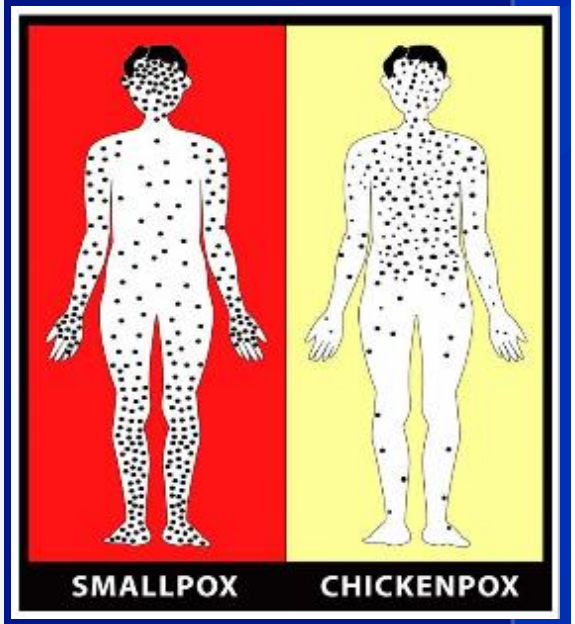
Acute, Generalized Vesicular or Pustular Rash Illness

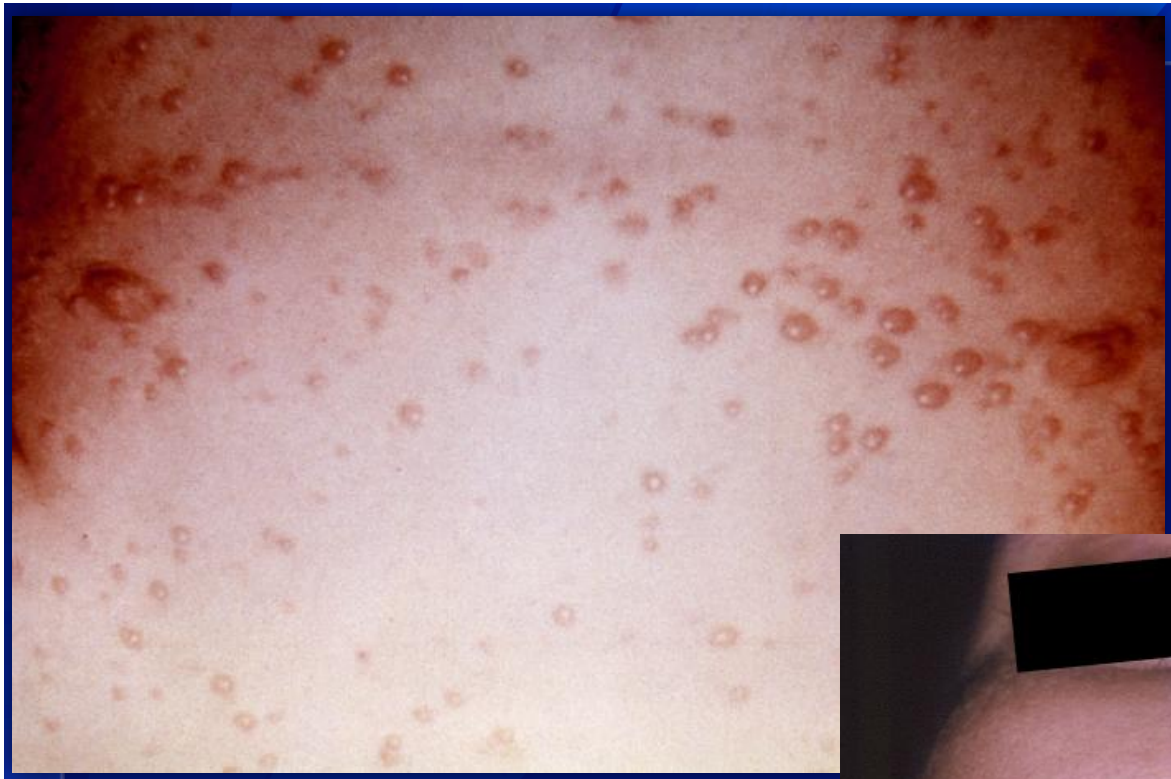
Differentiating Chickenpox from Smallpox

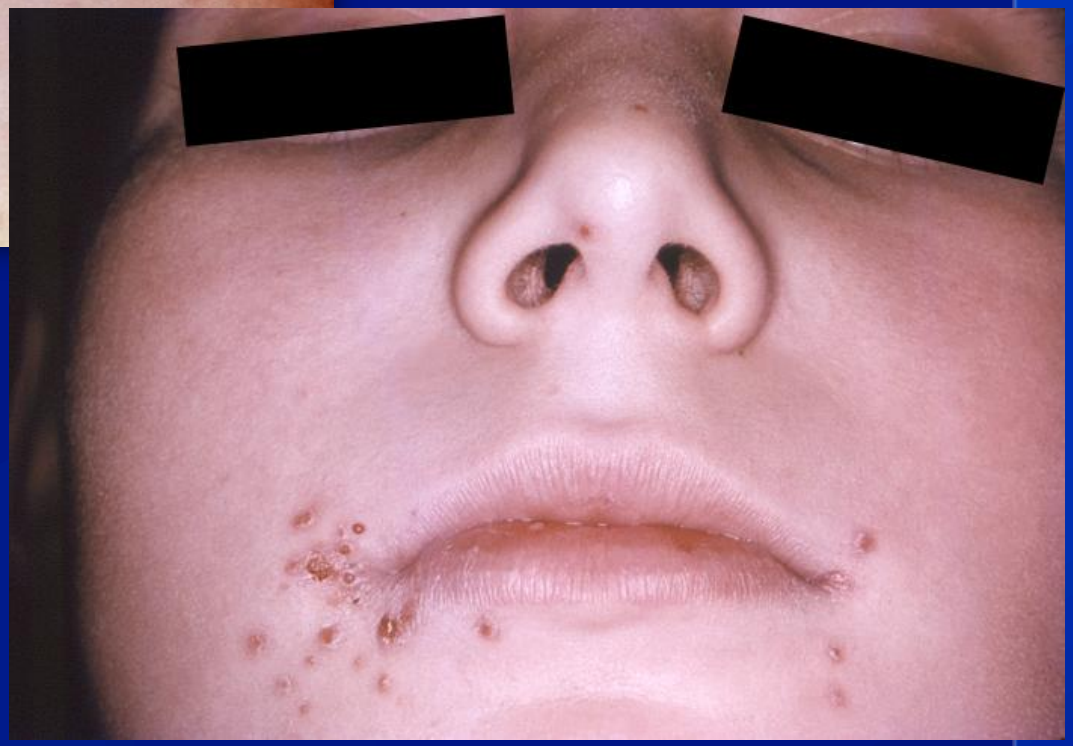
Chickenpox (varicella) is the most likely condition to be confused with smallpox.

In chickenpox:

- No or mild prodrome
- Lesions are superficial vesicles: "dewdrop on a rose petal" (see photo at top)
- Lesions appear in crops; on any one part of the body there are lesions in different stages (papules, vesicles, crusts)
- Centripetal distribution: greatest concentration of lesions on the trunk, fewest lesions on distal extremities. May involve the face/scalp. Occasionally entire body equally affected.
- First lesions appear on the face or trunk
- Patients rarely toxic or moribund
- Rapid evolution: lesions evolve from macules –> papules –> vesicles –> crusts quickly (<24 hours)
- Palms and soles rarely involved
- Patient lacks reliable history of varicella or varicella vaccination
- 50-80% recall an exposure to chickenpox or shingles 10-21 days before rash onset

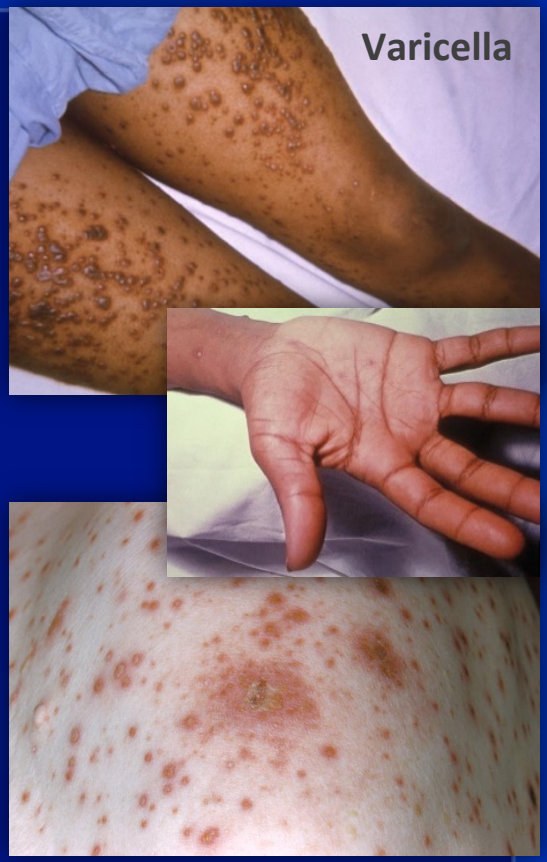


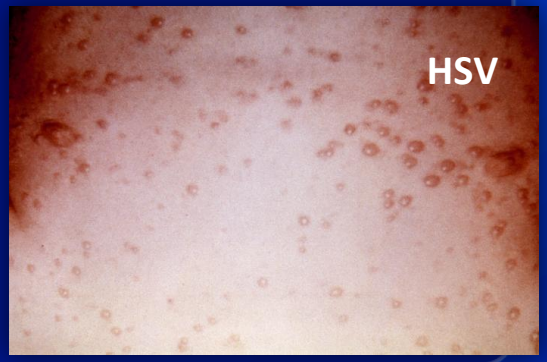


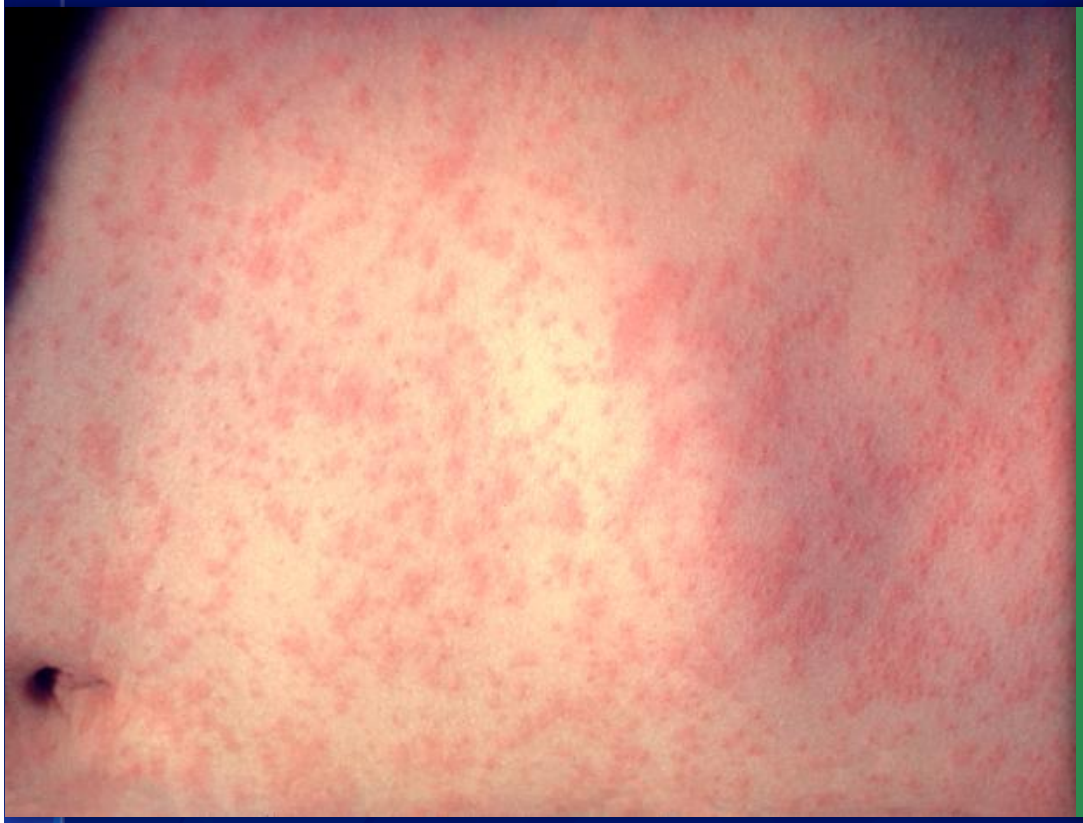


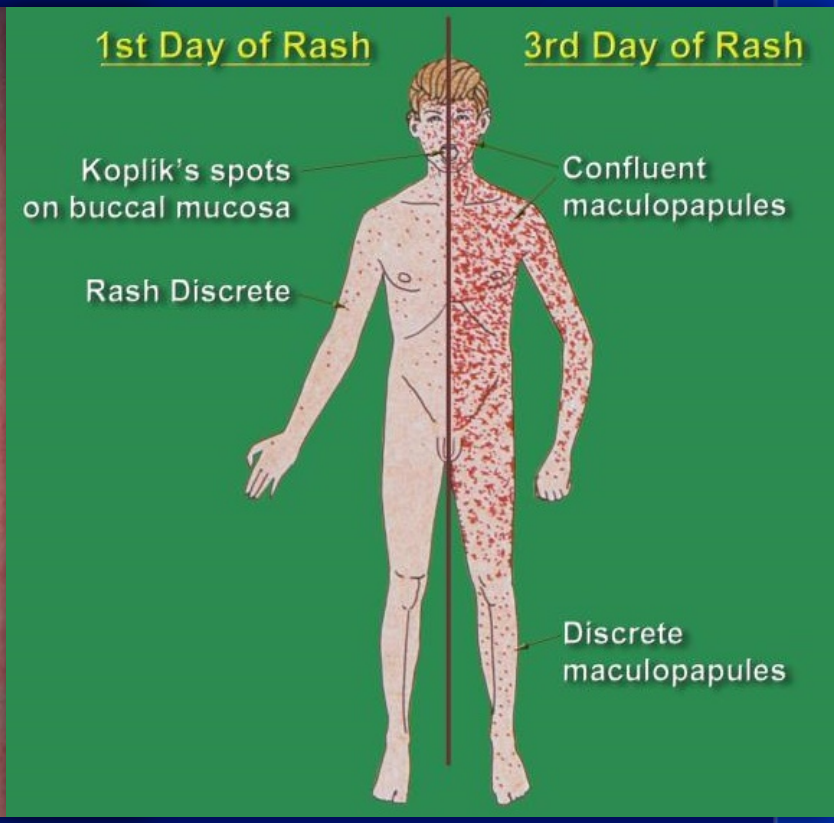
Herpes Simplex Virus

Disease	Chickenpox	Disseminated HSV
Causative agent	Varicella-zoster virus	Herpes Simplex Virus 1 or 2
Transmission	Respiratory droplets; aerosolized lesion fluid	Skin-to-skin
Incubation period	10-21 days	~7 days (range 1-26 days)
Fever before rash	Yes (1-2 days)	No (appear together)
Symptoms before rash	Malaise; headache	Malaise; myalgia; lymphadenopathy
Location first lesions	Head; chest; back	Often oral
Rash distribution	General; centripetal	Localized, sometimes generalized
Rash type	Macules; papules; vesicles; crusts	Vesicles
Rash duration	7-10 days	10-14 days (dependent on treatment)

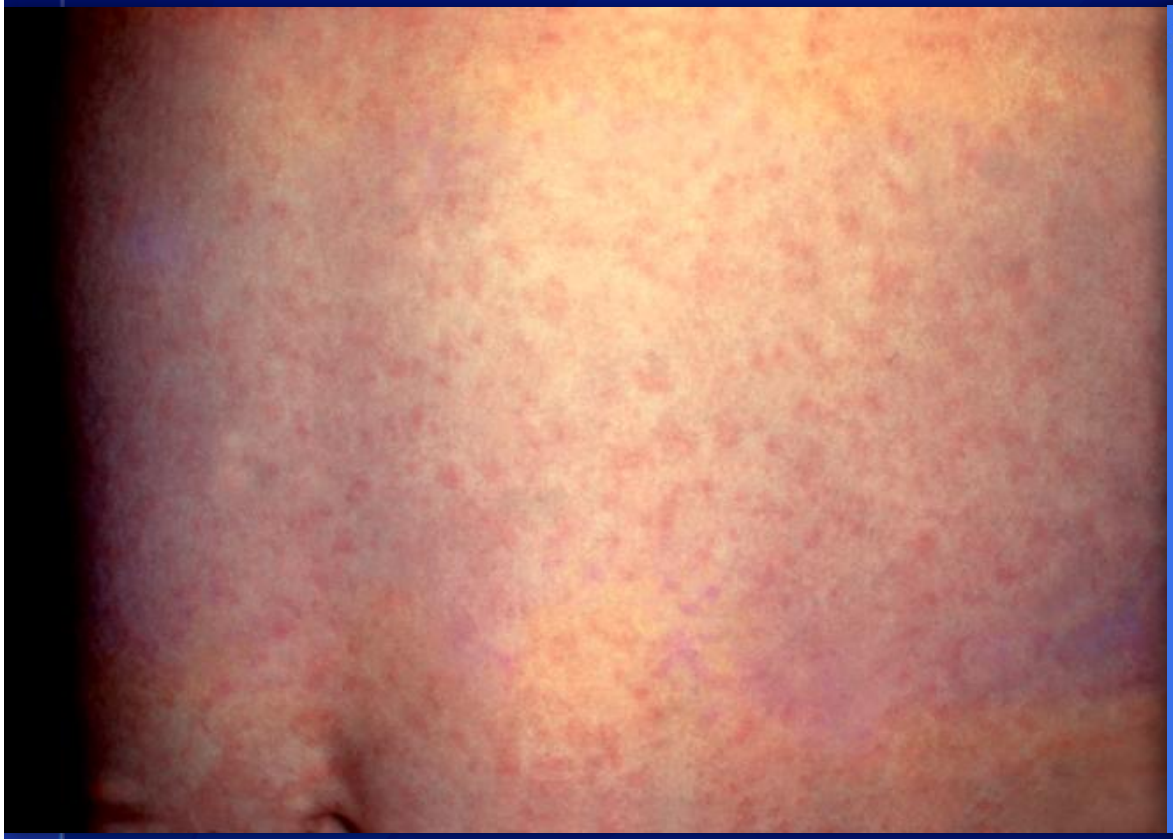


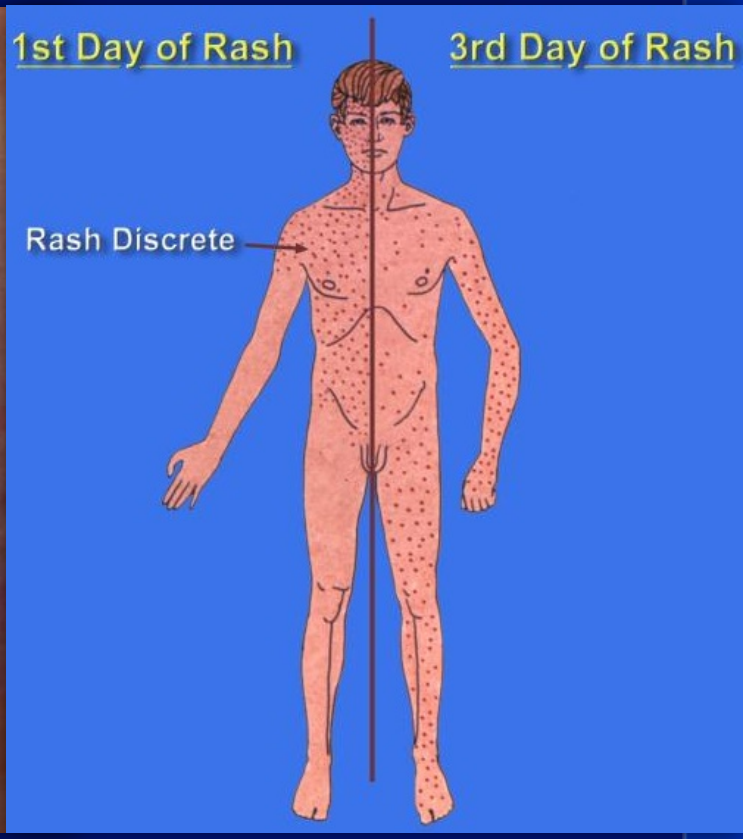





1st Day of Rash
3rd Day of Rash
Koplik's spots on buccal mucosa
Rash Discrete
Confluent maculopapules
Discrete maculopapules

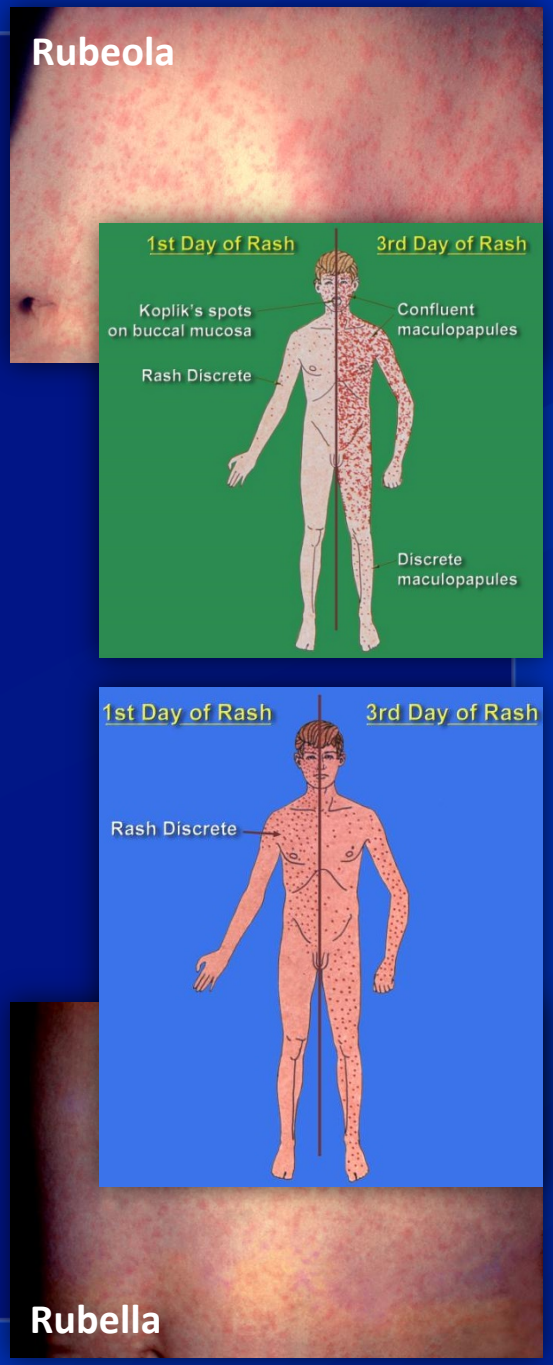
Rubeola



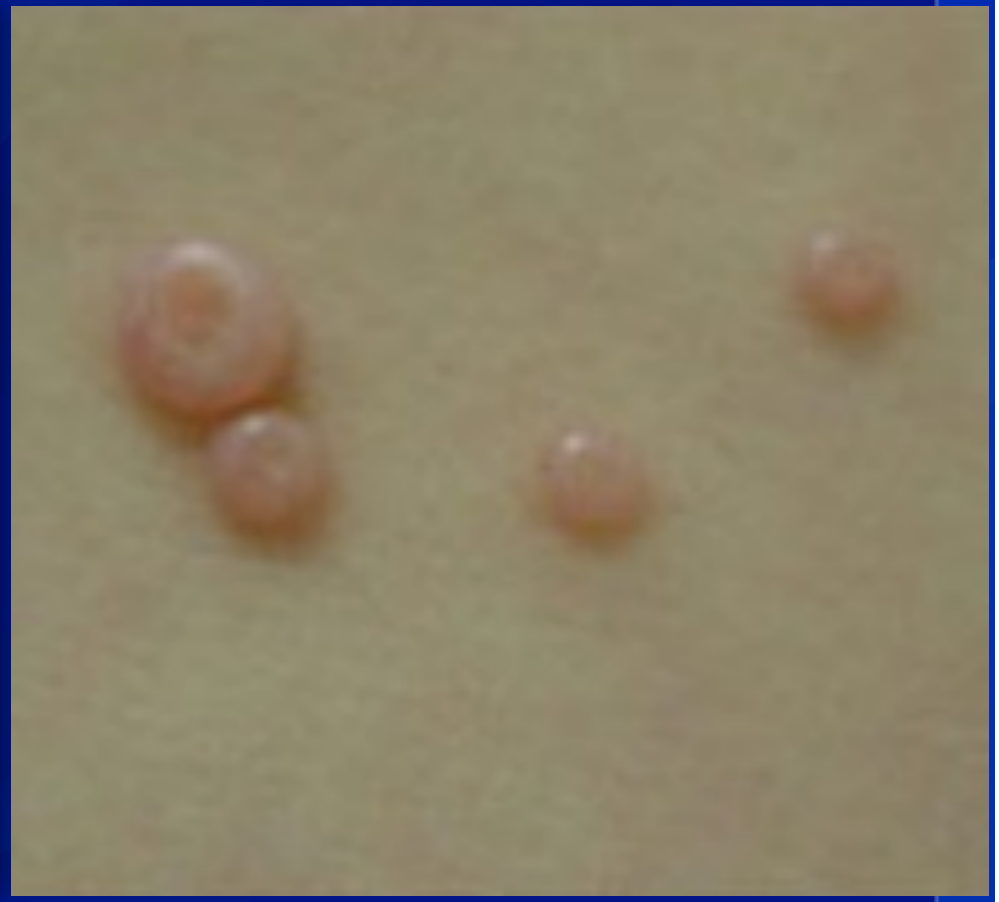


Rubella

Disease	Measles	German measles
Causative agent	Rubeola virus	Rubella virus
Transmission	Respiratory droplets	Respiratory droplets
Incubation period	10-12 days	14-21 days
Fever before rash	Yes (2-4 days)	Yes (≤24 hours)
Symptoms before rash	Cough; coryza; conjunctivitis	Malaise; headache
Location first lesions	Mouth (Koplik's spots); face	Neck; face
Rash distribution	General	General
Rash type	Maculopapular	Macules; maculopapular
Rash duration	5-6 days	24-48 hours

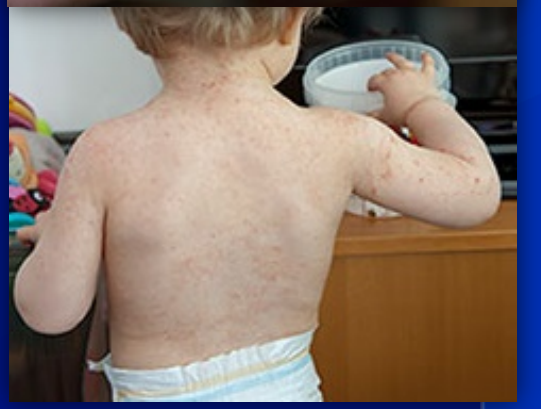


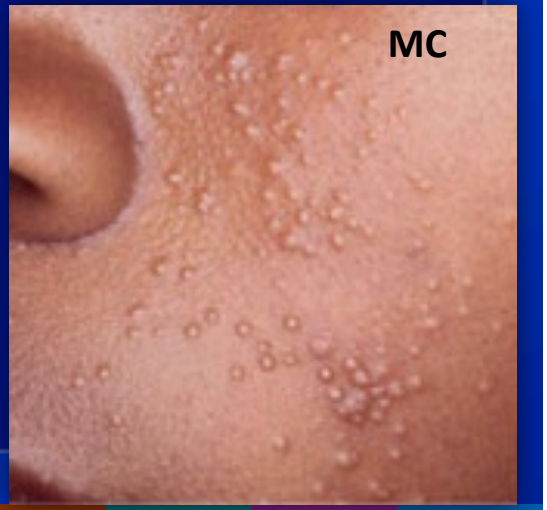
Hand Foot and Mouth Disease

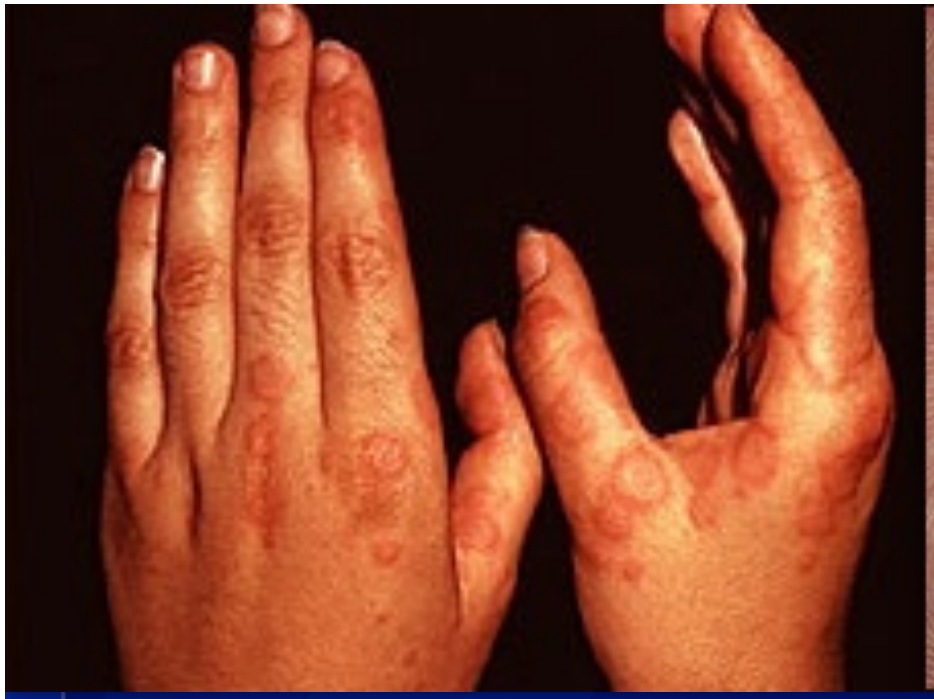


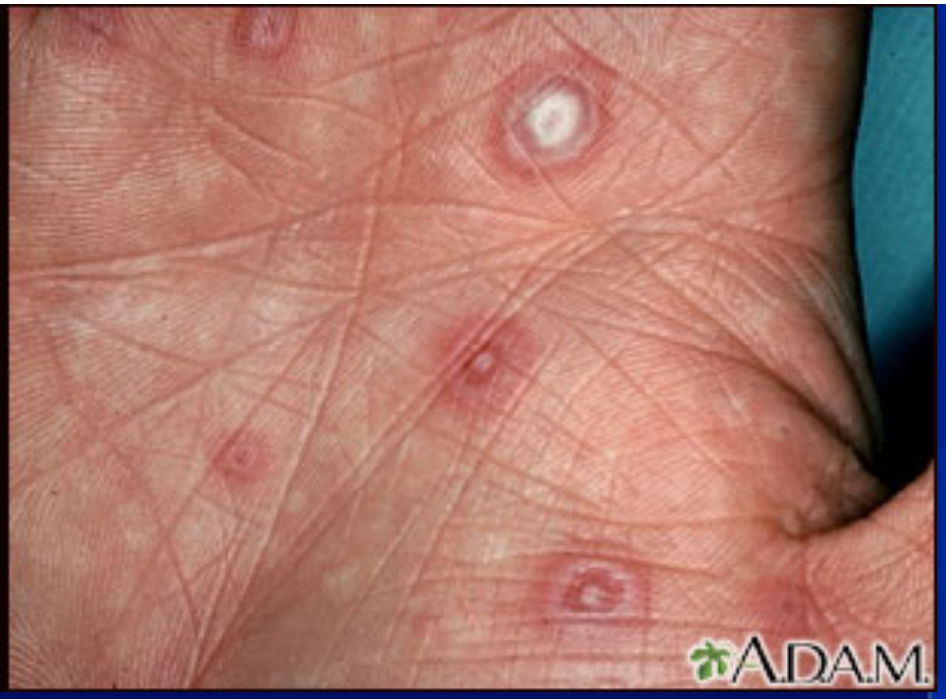
Molluscum Contagiosum

Disease	Hand, foot, and mouth	Molluscum contagiosum
Causative agent	Coxsackievirus A16; Enterovirus 71	MC virus
Transmission	Oral secretions; lesion fluid; feces	Skin-to-skin; fomites
Incubation period	3-6 days	Unknown
Fever before rash	Yes (1-2 days)	No
Symptoms before rash	Sore throat; malaise	None
Location first lesions	Mouth	Anywhere
Rash distribution	Mouth; palms; soles; other areas	Grouped
Rash type	Macules; vesicles	Papules
Rash duration	7-10 days	Weeks to months

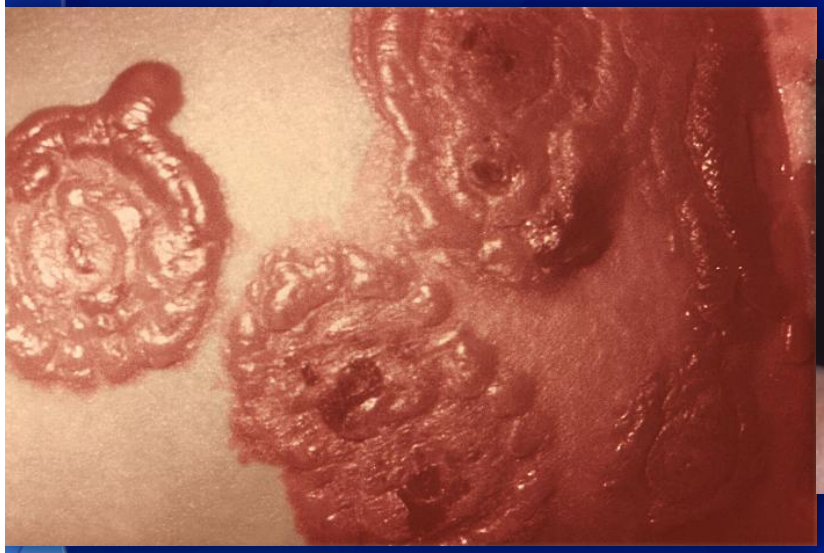


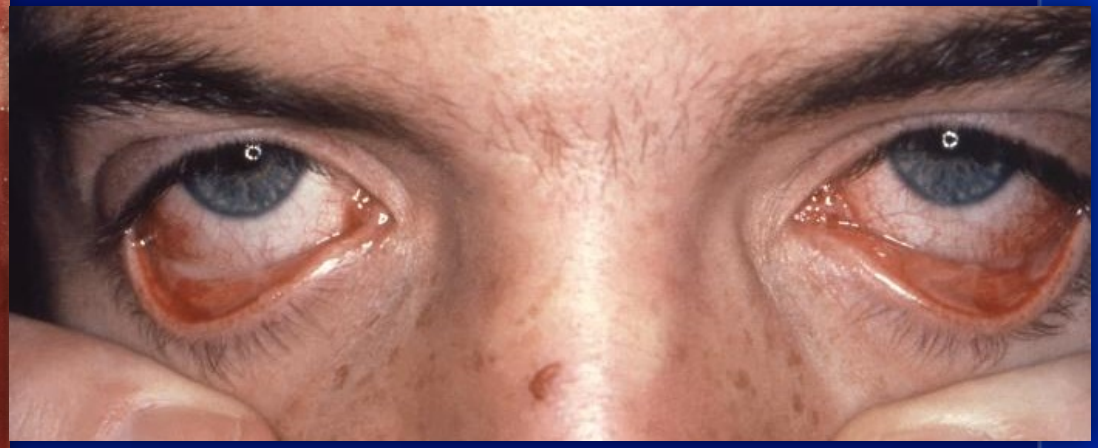






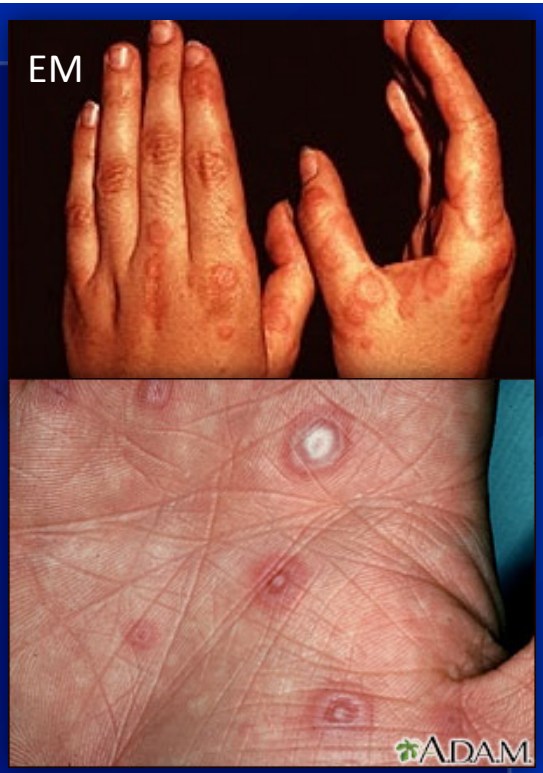
Erythema Multiforme

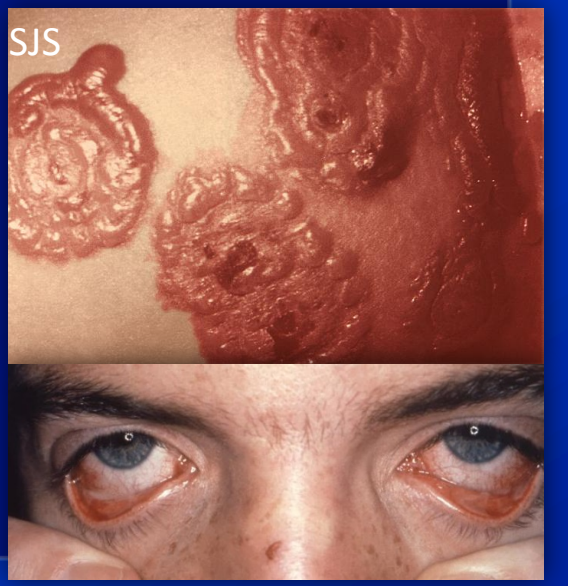


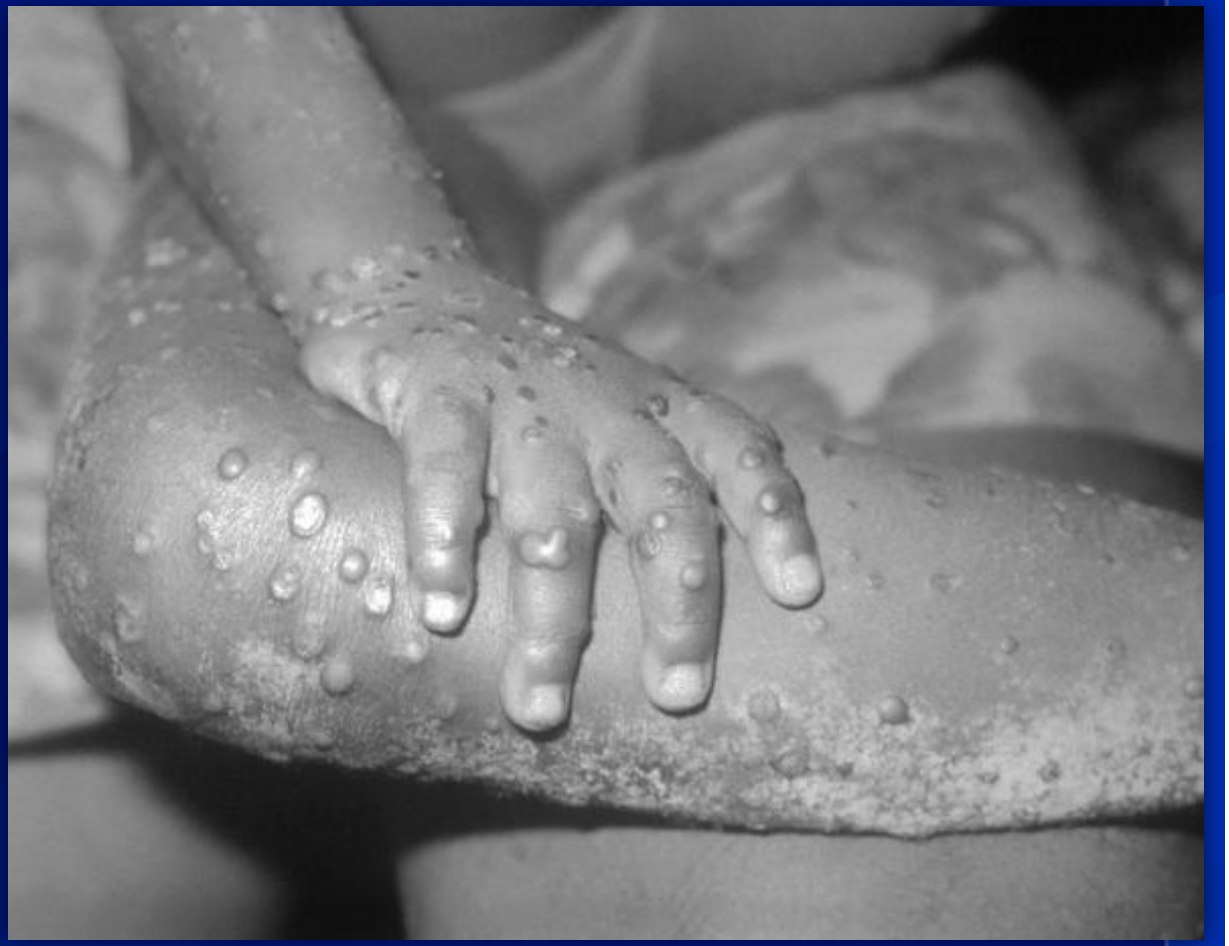


Stevens Johnson Syndrome

Disease	Erythema multiforme	Stevens-Johnson Syndrome
Causative agent	Hypersensitivity reaction	Hypersensitivity reaction
Transmission	None	None
Incubation period	3-10 days	Days to 2 months
Fever before rash	Varies with severity	Yes (1-3 days)
Symptoms before rash	Varies with severity	Flu-like
Location first lesions	Dorsal hands, feet	Face; chest
Rash distribution	General	General
Rash type	Target; vesicles	Macules; target; bullae
Rash duration	2-6 weeks	8-12 days



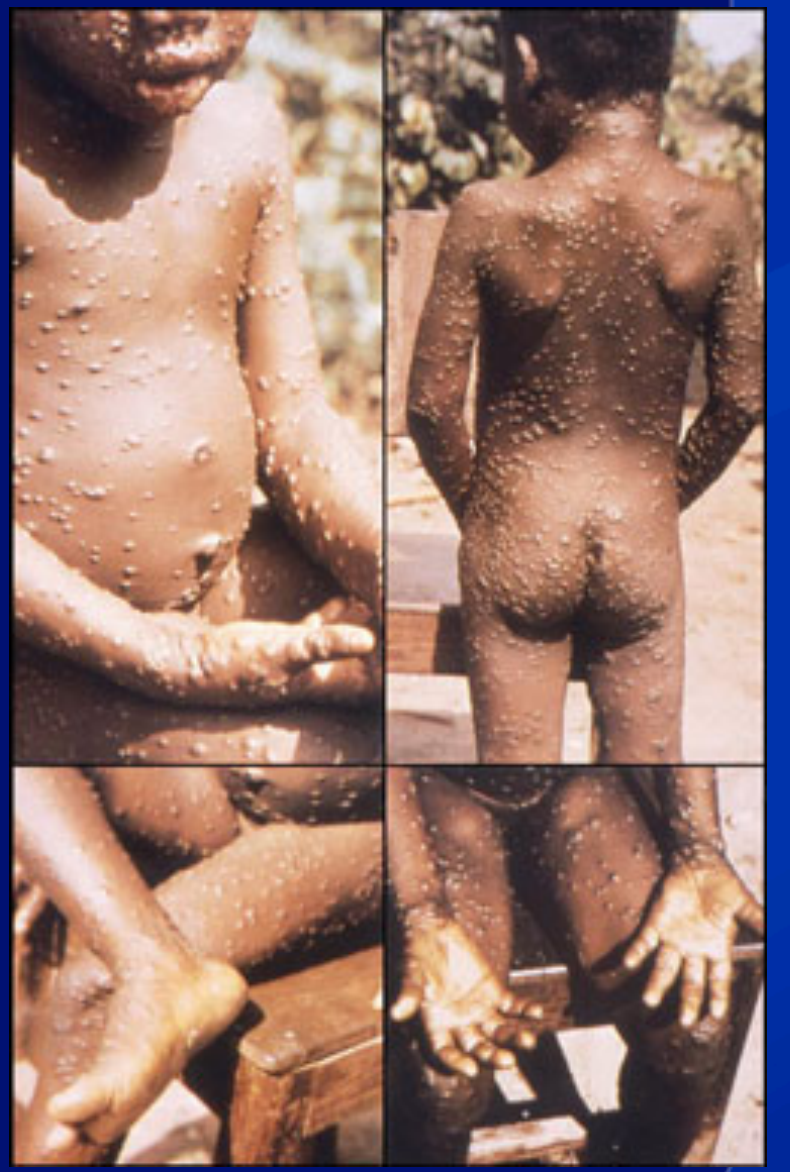




Monkeypox

Monkeypox

- Causative agent: *monkeypox virus*
- Clinical presentation: disseminated vesicular/pustular rash associated with fever, malaise, and lymphadenopathy
- Transmission: primarily zoonotic following contact with infected animals; human-to-human via respiratory droplets and lesion exudates
- Animal reservoir: likely small rodents (rope squirrel, Gambian rat, dormouse)



Routes of infection

Animal source/material transmission:

Via the oropharynx or nasopharynx; through abrasions of the skin or oral cavity

Person-to-person transmission:

Upper respiratory tract by inhalation or implantation; by inoculation through the skin; rarely, via the placenta

Incubation

Prodrome

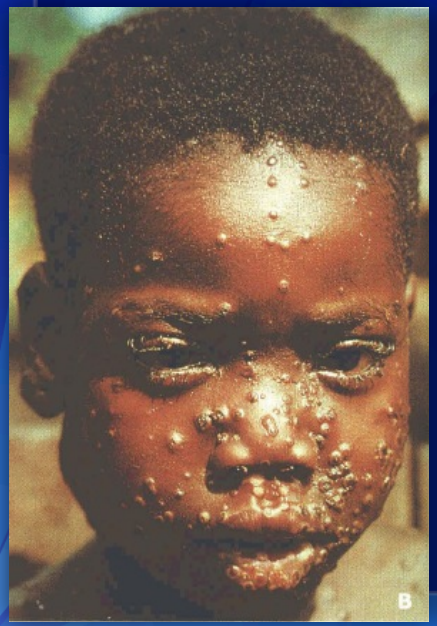
Presentation of first symptoms: fever, malaise, headache, myalgia, lymphadneopathy

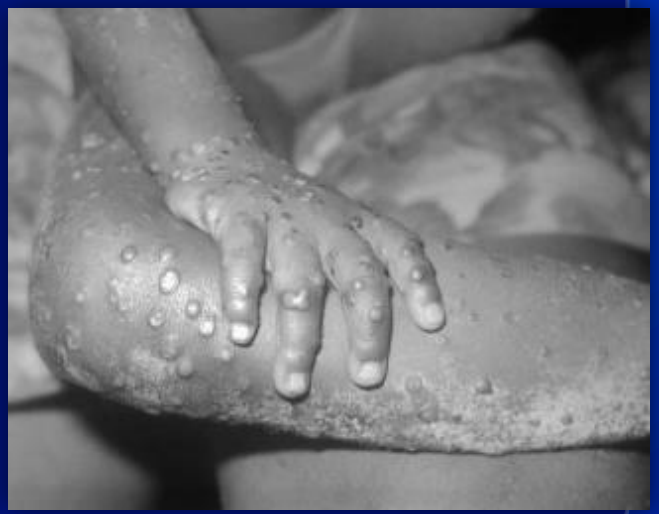
Rash

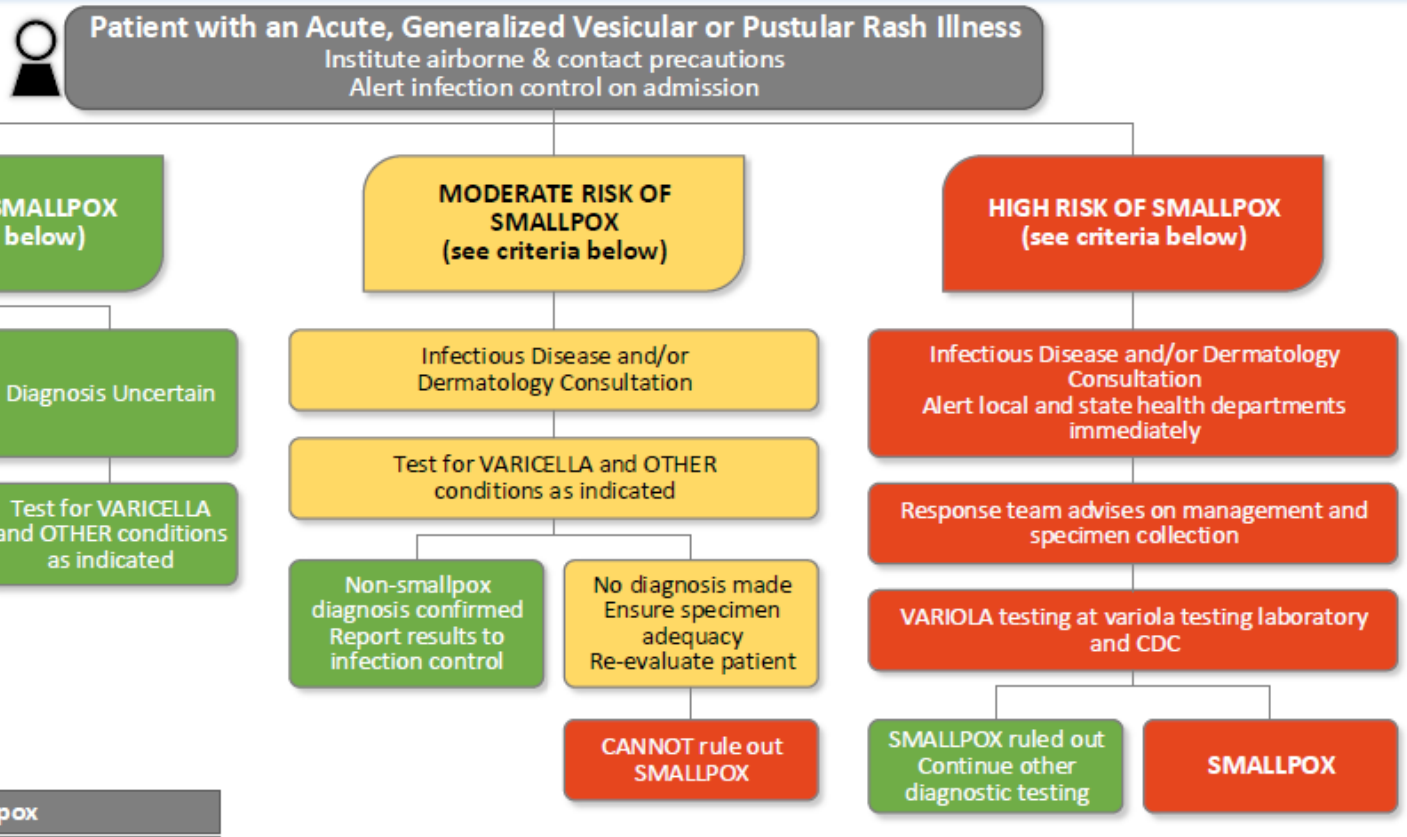
Lesions on mucosa

Rash appearance and progression similar to discrete ordinary-type smallpox

Pustules begin to crust and scab then fall off







Risk of Smallpox
HIGH RISK OF SMALLPOX • Febrile prodrome AND • Classic smallpox lesions AND • Lesions in same stage of development in any one area of the body
MODERATE RISK OF SMALLPOX • Febrile prodrome **AND** one other MAJOR smallpox criterion OR • Febrile prodrome **AND** ≥4 MINOR criteria
LOW RISK OF SMALLPOX • No febrile prodrome OR • Febrile prodrome AND <4 MINOR criteria

MAJOR Smallpox Criteria
• **Febrile prodrome:** Fever of ≥101°F, 1-4 days prior to rash onset with at least prostration, headache, backache, chills, vomiting or severe abdominal pain
• **Classic smallpox lesions:** Deep-seated, firm/hard, round well-circumscribed vesicles of pustules; lesions may umbilicate or become confluent
• **Lesions in same stage of development:** On any one part of the body all lesions in same stage of development

MINOR Smallpox Criteria
• Centrifugal distribution of lesions
• First lesions on the oral mucosalpalate, face, or forearms
• Patient appears toxic or moribund
• Slow evolution of lesions from macule, to papule, to vesicle (1-2 days each stage)
• Lesions on the palms and soles

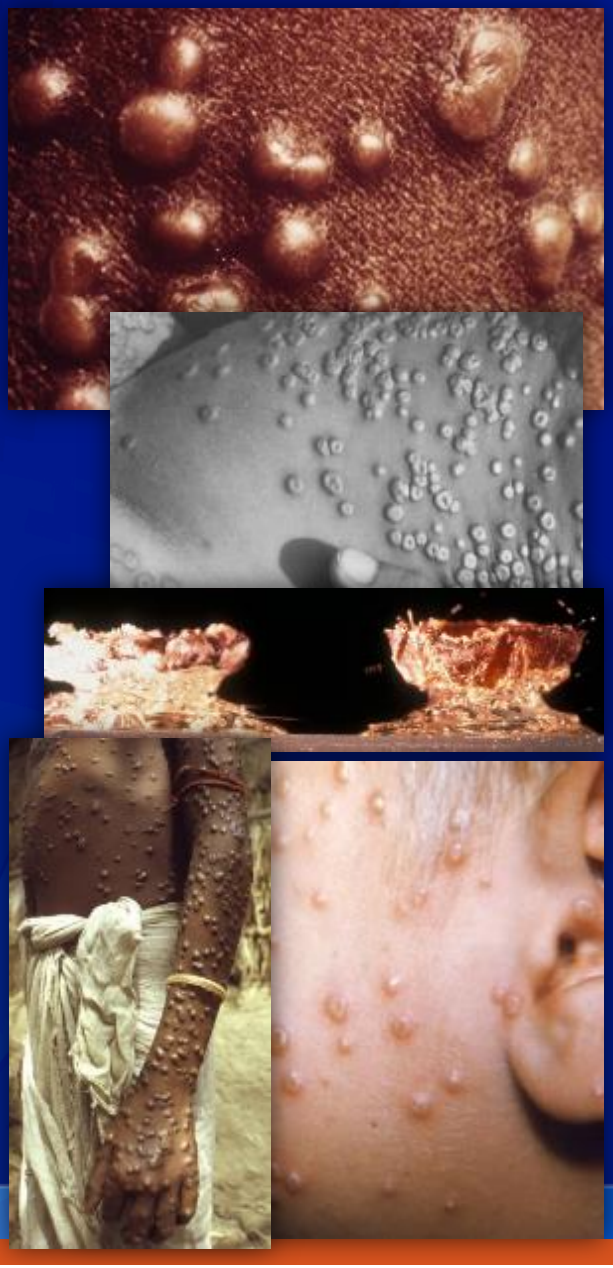
The poster, *Evaluating Patients for Smallpox: Acute, Generalized Vesicular or Pustular Rash Illness Protocol*, can be found on CDC's smallpox website.

https://www.cdc.gov/smallpox/clinicians/algorithm-protocol.html

Immediate Action for Patient with Acute, Generalized Vesicular or Pustular Rash Illness

- Institute airborne and contact precautions
- Alert infection control team

Acute, Generalized Vesicular or Pustular Rash Illness



HIGH RISK

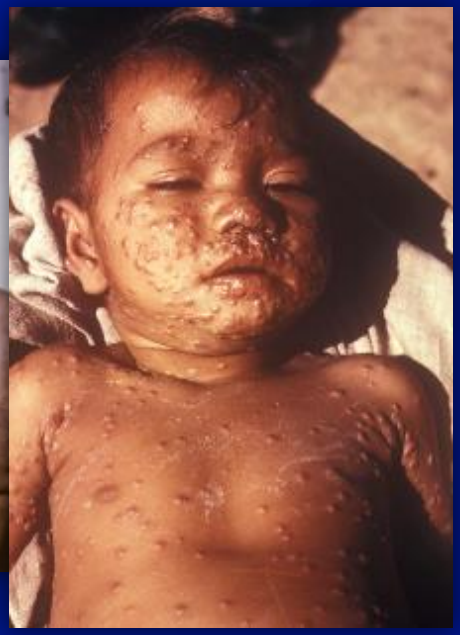
- Febrile prodrome **AND**
- Classic smallpox lesions **AND**
- Lesions in same stage of development

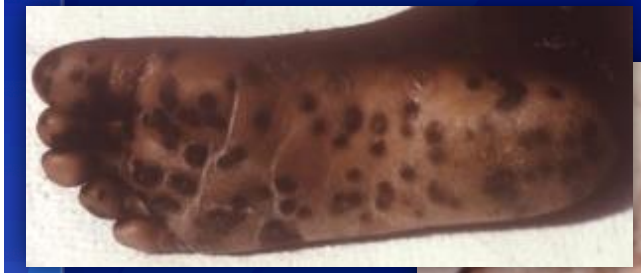
Febrile prodrome:
Fever of ≥101°F, 1–4 days prior to rash onset with at least prostration, headache, backache, chills, vomiting or severe abdominal pain

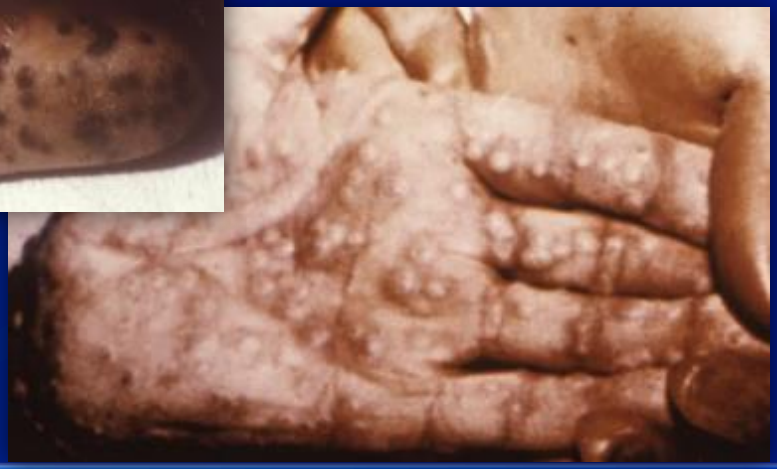
Classic smallpox lesions:
Deep-seated, firm/hard, round well-circumscribed vesicles or pustules; lesions may umbilicate or become confluent

Lesions same stage of development:
On any one part of the body all lesions in same stage of development

Acute, Generalized Vesicular or Pustular Rash Illness







MODERATE RISK

- Febrile prodrome **AND** one other major criterion **OR**
- Febrile prodrome **AND** ≥4 minor criteria

LOW RISK

- No febrile prodrome **OR**
- Febrile prodrome **AND** <4 minor criteria

Minor criteria:

- Centrifugal distribution: greatest concentration of lesions on face and extremities
- First lesions on the oral mucosal palate, face or forearms
- Toxic or moribund
- Slow rash evolution (evolve from macules -> papules -> pustules over days (1-2 days each)
- Lesions on the palms and soles

Response

- **High Risk Case – Report Immediately**
  - Infectious diseases +/- dermatology consultation to confirm high risk status
  - Alert health department + CDC immediately
  - Laboratory testing for variola virus at CDC +/- LRN
- **Moderate Risk Case - Urgent Evaluation**
  - Infectious diseases +/- dermatology consultation
  - Laboratory testing for varicella and other diseases at local or state level
    +/- CDC as requested
  - Digital photos are useful
  - Re-evaluated at least daily to determine if risk level altered
- **Low Risk Case – Manage as Clinically Indicated**
  - Test for VZV and other conditions as clinically indicated

Acute, Generalized Vesicular or Pustular Rash Illness

Common Conditions That Might Be Confused With Smallpox

Condition	Clinical Clues
Varicella (primary infection with varicella-zoster virus)	Most common in children <10 years; children usually do not have a viral prodrome
Disseminated herpes zoster	Immunocompromised or elderly persons; rash looks like varicella, usually begins in dermatomal distribution
Impetigo *(Streptococcus pyogenes, Staphylococcus aureus)*	Honey-colored crusted plaques with bullae are classic but may begin as vesicles; regional not disseminated rash; patients generally not ill
Drug eruptions	Exposure to medications; rash often generalized
Contact dermatitis	Itching; contact with possible allergens; rash often localized in pattern suggesting external contact
Erythema multiforme minor	Target, "bull's eye", or iris lesions; often follows recurrent herpes simplex virus infections; may involve hands & feet (including palms & soles)
Erythema multiforme (incl. Stevens Johnson Syndrome)	Major form involves mucous membranes & conjunctivae; may be target lesions or vesicles
Enteroviral infection esp. Hand, Foot and Mouth disease	Summer & fall; fever & mild pharyngitis 1-2 days before rash onset; lesions initially maculopapular but evolve into whitish-grey tender, flat often oval vesicles; peripheral distribution (hands, feet, mouth, or disseminated)
Disseminated herpes simplex	Lesions indistinguishable from varicella; immunocompromised host
Scabies; insect bites (incl. fleas)	Itching is a major symptom; patient is not febrile & is otherwise well
Molluscum contagiosum	May disseminate in immunosuppressed persons

Laboratory detection of poxviruses

Genus specific:

Viral culture

- Presence of cytopathic effect (CPE), cytoplasmic projections, and syncytia

Electron microscopy (EM)

- Direct examination of clinical material using an electron microscope for rapid identification of virus particles
- Can readily differentiate a poxvirus infection from another virus

Immunohistochemical staining (IHC)

- Visualization of an antigen-antibody interaction

Serology

- Antibody detection alone cannot confirm a diagnosis but can be highly suggestive of infection if a 4-fold rise in antibody titer is seen
- Antibodies can be detected by hemmaglutination (HA), neutralization, enzyme-linked immunosorbent assay (ELISA), radioimmunoassay (RIA), indirect immunofluorescence tests, or plaque reduction neutralization tests (PRNT).

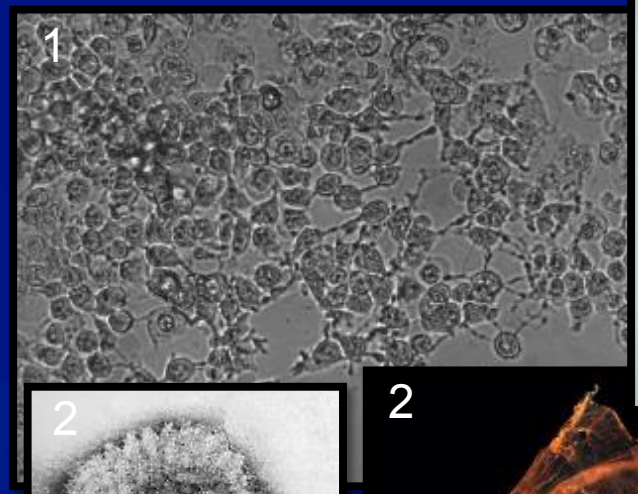
Species specific:

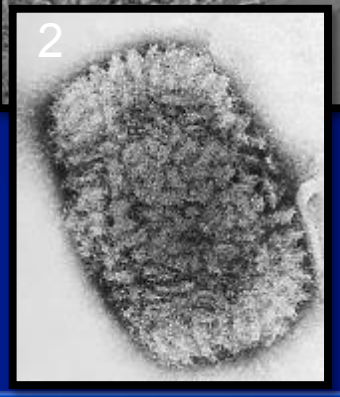
Chorioallantoic membrane (CAM)

- Production of hemorrhagic pock marks on the surface of the membrane

Polymerase Chain Reaction (PCR)

- Standard
- Real-time





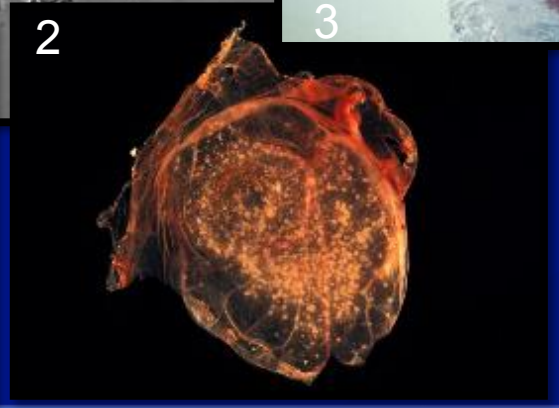


Image 1 from the Poxvirus and Rabies Branch
Image 2 from Courtesy of CDC's Public Health Image Library
Image 3 from Guarner J, *et al*. Monkeypox transmission and pathogenesis in prairie dogs. Emerg Infect Dis. 2004 Mar;10(3):426-31.

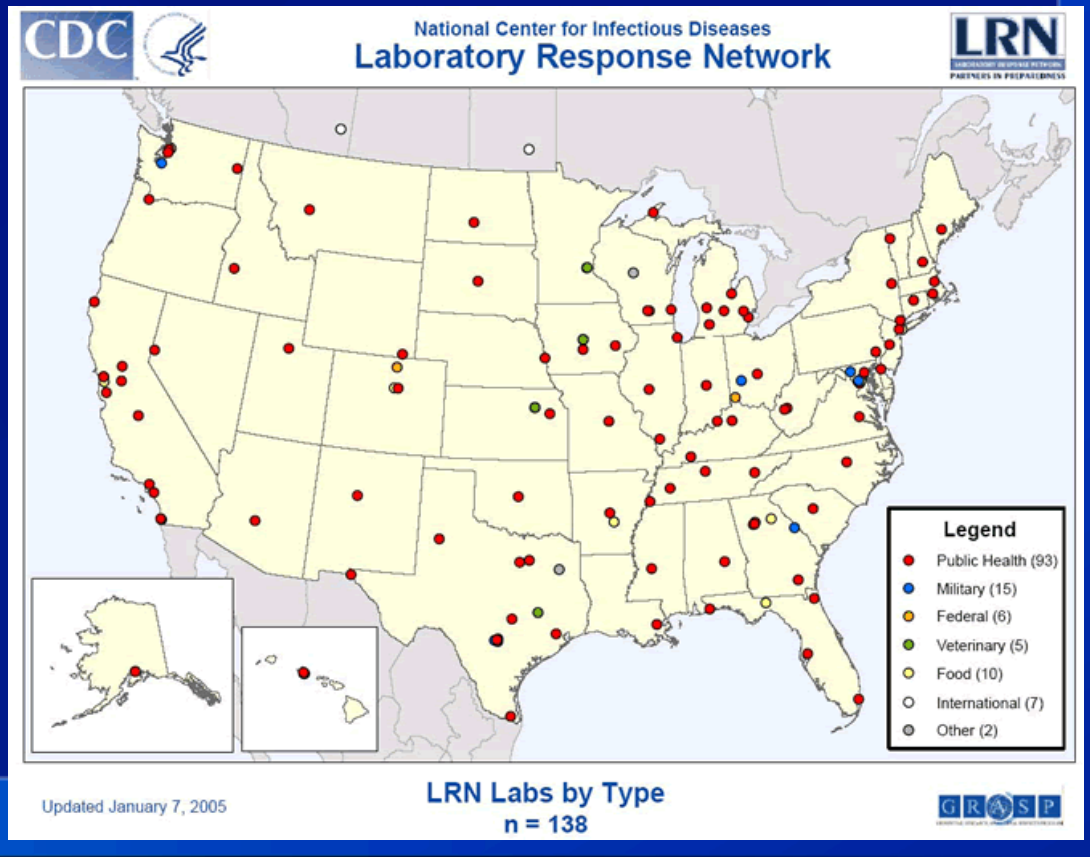
Specimen Collection

Disease Phase	Specimens to Collect
Prodrome	Tonsillar tissue swab Nasopharyngeal swab Acute serum and whole blood
Rash*	
Macules or Papules	Tonsillar tissue swab Lesion biopsy Acute serum and whole blood
Vesicles or Pustules	Lesion fluid, roof, or biopsy Acute serum and whole blood Electron microscopy grid (if supplies available)
Scabs or Crusts	Lesion scab or crust Acute serum and whole blood
Post-Rash	Convalescent serum
* More than one lesion should be sampled, preferably from different locations on the body and/or from different looking lesions.	

https://www.cdc.gov/poxvirus/monkeypox/clinicians/prep-collection-specimens.html

Laboratory Response Network (LRN)

- Integrated network of laboratories
  - State and local public health
  - Federal (United States)
  - Military
  - International
- Respond to bioterrorism and other public health emergencies



Bayes' Theorem and Diagnostic Tests

- **The probability of event A given event B**

$$P(A|B) = P(A) \times P(B|A) / P(B)$$

- **P(A) is the probability of disease (dependent on prevalence)**
- **P(B) is the probability of a positive test (dependent on sensitivity and specificity**

		Disease		
		Present	Absent	Total
Test result	POS	A = true positives	B = false positives	A +B
	NEG	C = false negative	D = true negative	C + D
	TOT	A + C	B + D	

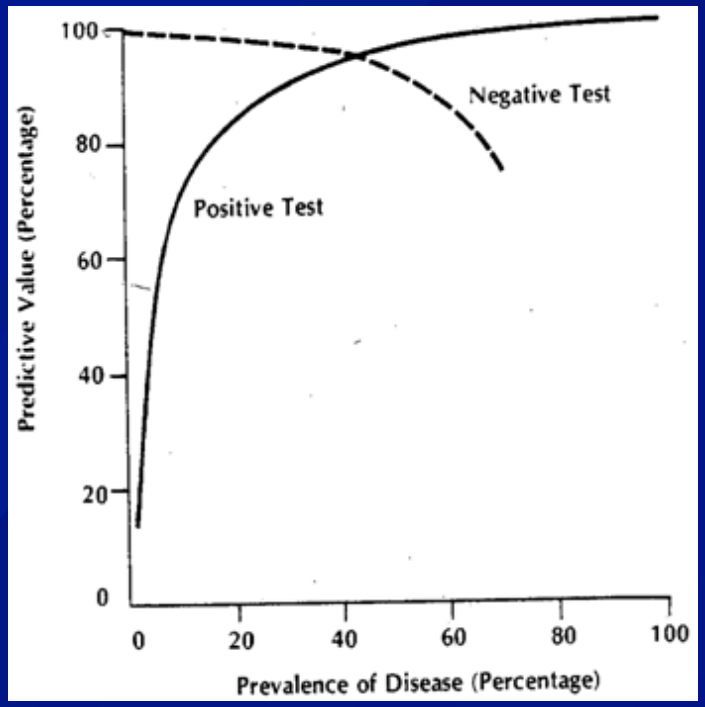
Positive Predictive Value = A / (A + B)

Negative Predictive Value = D / (C + D)

Sensitivity = A / (D + C)

Specificity = D / (B + D)

Bayes' Theorem and Diagnostic Tests



Sensitivity 99%

Specificity 99%

Prevalence	Positive Predictive Value	Negative Predictive Value
10%	92.8%	99.8%
1%	50%	99.99%
0.1%	9%	100%

Scenario 1

A 9-year-old male with no significant past medical history presented to his pediatrician with a one-week history of ulcerations of the oral mucosa followed by development of dermal lesions. Prior to rash formation, the patient was febrile per subjective evaluation by his mother (not measured) and had sore throat, chills and malaise. The patient was not on any medications including over-the-counter medications. Oral examination revealed multiple ulcerations on the lips and gums, as well as swelling of the upper lip, and fissuring and cracking at both corners of the mouth. Left and right cervical lymph nodes were palpable and tender. Dermal examination revealed lesions on the dorsal and palmar surfaces of the hands, extensor aspects of the upper and lower extremities, and plantar surfaces of both feet. Lesions of various morphologies were present: 1) round and sharply demarcated lesions with a dusky red center, paler pink edematous edges, and with or without bright erythematous peripheral ring, and 2) vesicles with central crusting. Vital signs and complete blood count were within normal limits.

MAJOR

Febrile prodrome:	Maybe
Classic lesions:	No
Same development stage:	No

MINOR

Centrifugal distribution:	Unknown
First lesions oral mucosal palate, face or forearms:	Yes
Toxic or moribund:	Unknown
Slow rash evolution:	Unknown
Lesions on palms/soles:	Yes
Diagnosis:	Erythema multiforme

Scenario 2

A 19-year-old female with no significant past medical history presented to her primary care physician on the morning of February 20 with a three-day history of pyrexia, headache, and episodes of vomiting. Temperature measured 40°C at presentation but remaining vital signs were within normal limits. The patient was diagnosed with influenza, prescribed oseltamivir, and discharged. Later that same evening, the patient complained of a sore throat and non-productive cough. The following day, the patient developed a macular rash on her face. After consultation with her PCP, oseltamivir was discontinued. Over the next 24 hours, the rash spread over the entire body and lesions on the face were progressing to papules. Four days after onset of rash, lesions were small, discrete vesicles. By day five of rash, pustules were unilocular, with greatest concentration on the face and distal arms and legs. A few lesions were evident on the plantar and palmar surfaces. Lesions began crusting seven days post onset.

MAJOR

Febrile prodrome:	Yes
Classic lesions:	Unknown
Same development stage:	Unknown

MINOR

Centrifugal distribution:	Yes
First lesions oral mucosal palate, face or forearms:	Yes
Toxic or moribund:	Not mentioned
Slow rash evolution:	Yes
Lesions on palms/soles:	Yes
Diagnosis:	Variola minor

Questions?

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For more information please contact Centers for Disease Control and Prevention

Telephone: 1-800-CDC-INFO (232-4636)/TTY: 1-888-232-6348

E-mail: cdcinfo@cdc.gov Web: http://www.cdc.gov