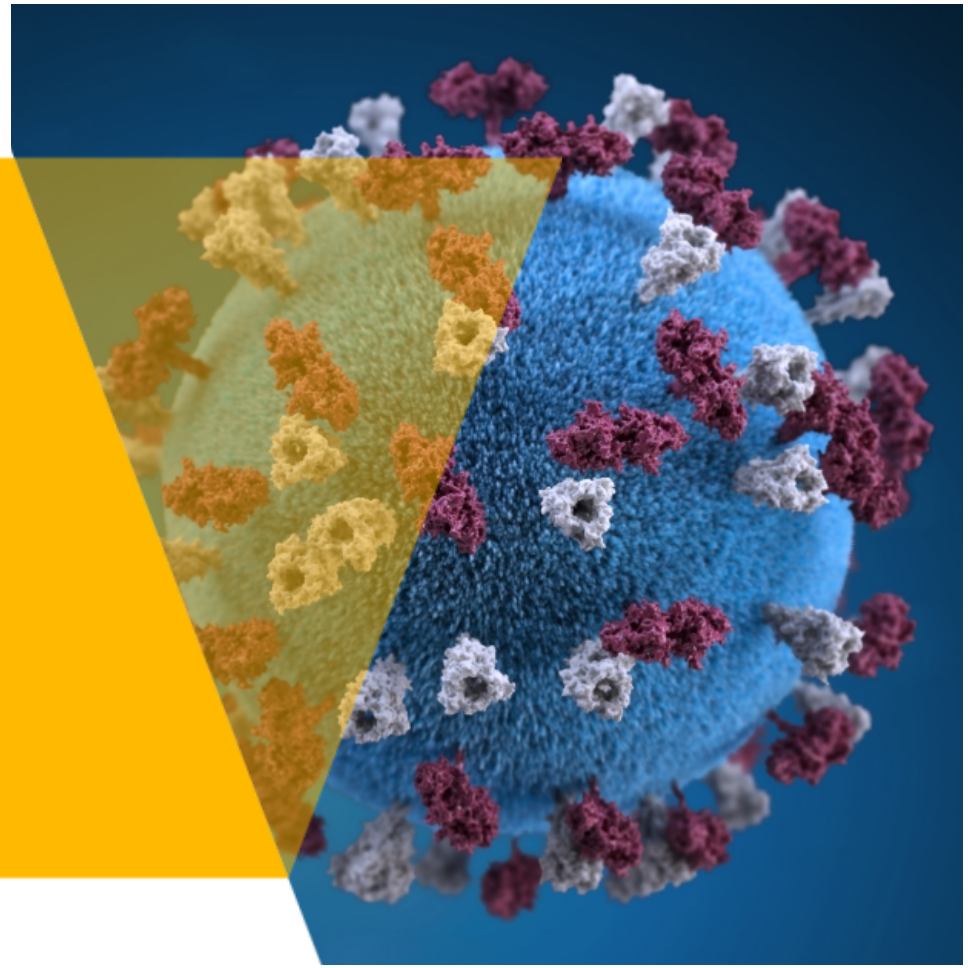
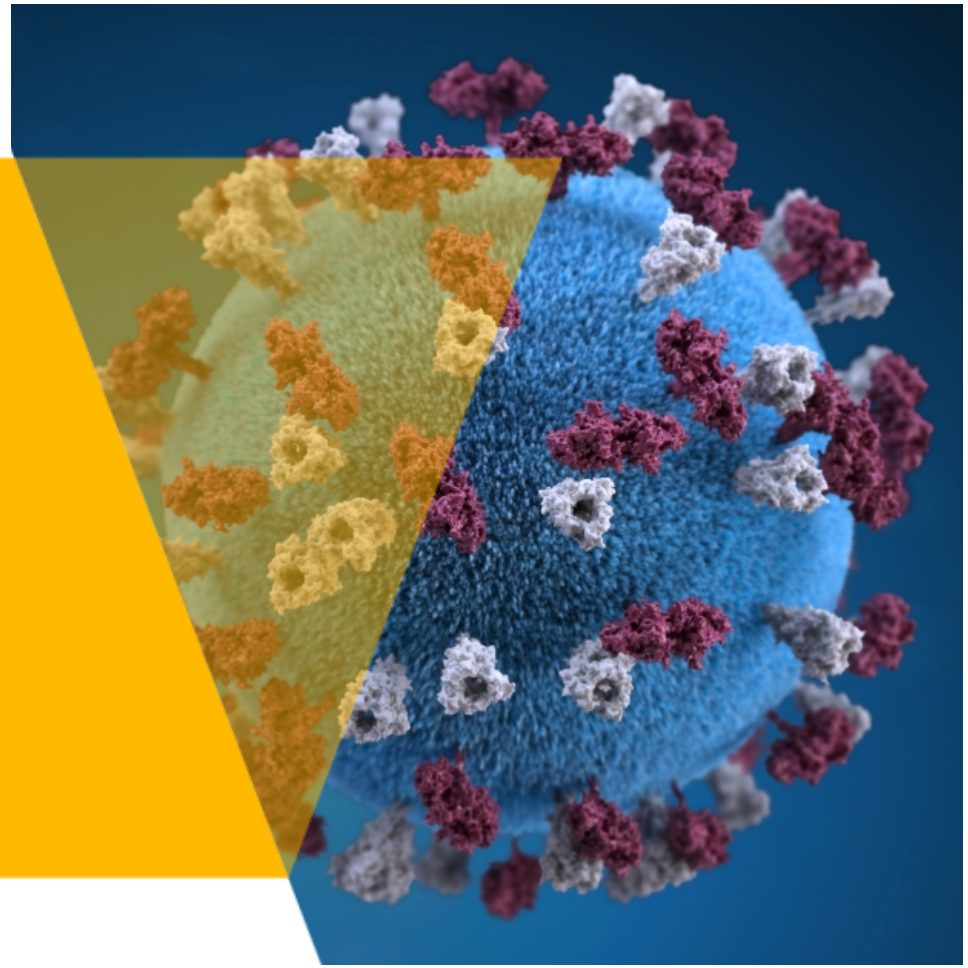
The session will begin momentarily.

Recognition of Infectious Diseases in Refugees and Infection Prevention Considerations



October 28, 2021

Recognition of Infectious Diseases in Refugees and Infection Prevention Considerations



October 28, 2021

Virginia Infection Prevention Training Center

What is the VIPTC?

- Virginia Commonwealth University (VCU) and Virginia Department of Health (VDH) partnership to establish infection prevention education and training to support healthcare facilities of all types
- Curriculum design will be targeted to level of existing infection prevention (IP) expertise (if any) and site-specific
    - Full course content available beginning early 2022
    - Introductory Webinars for current issues in IP monthly
- Contact us!
    - VIPTC@vcuhealth.org
    - Sign up for our list-serve (via above email)
    - Send us your ideas for course content and areas of need
    - Visit our webpage:

https://www.vcuhealth.org/explore-vcu-health/for-health-professionals/virginia-infection-prevention-training-center

VCU Health

All Images used in this presentation are from the Public Health Image Library: https://phil.cdc.gov/

No Conflicts of Interest

Infections potentially occurring in returning travelers or evacuees:

Potentially contagious within the healthcare system:

Respiratory:
- COVID-19
- **Measles***
- **Mumps***
- **Rubella***
- Tuberculosis
- **Diphtheria***
- Pertussis

Gastrointestinal:
- Cholera
- Hepatitis A, B, E

Other:
- Typhoid fever
- **Polio***
- **Rabies***

Standard Precautions:

1. **Perform Hand Hygiene**
2. Use PPE whenever there is expectation of a possible exposure to infectious material
    - wound care
    - respiratory care
    - bedside procedures
    - handling body fluids/risk of splash
3. Follow respiratory hygiene/cough etiquette
4. Ensure appropriate patient placement – i.e., private rooms and transmission based precautions if applicable
5. Properly handle, clean, disinfect patient care equipment, including instruments/devises AND clean/disinfect the environment
6. Handle textile and laundry carefully
7. Follow safe injection practices
    - wear surgical/droplet masks when performing lumbar punctures

https://www.cdc.gov/oralhealth/infectioncontrol/summary-infection-prevention-practices/standard-precautions.html

Transmission-based Precautions (Isolation Precautions)

Based on the **most important mechanism** of transmission epidemiologically

i.e., How the infection is *generally* transmitted person-to-person in real life

However, even if Contact Precautions (PPE requirements for gown/gloves) are NOT specifically recommended, many of these infections are **readily passed person-to-person on healthcare provider hands** if given the opportunity, particularly in healthcare settings – thus Standard Precautions are critically important components of care for patients on Airborne or Droplet Precautions!

Measles

One of the most contagious infections that exists:

- **R_0 is calculated to be 12-14**, meaning one person infects on average 12-14 additional people during the course of their illness, if population is susceptible
- Attack rate in susceptible persons exposed is 90%
- Transmission is via Respiratory Droplets and secretions:
- **Airborne spread** has been convincingly documented
- Infectious “a few days before” rash onset to 4 days after rash appears (rash onset=day 0), infectious period can be longer in immunosuppressed persons

American Academy of Pediatrics. Committee on Infectious Diseases. Red Book : Report of the Committee on Infectious Diseases. Elk Grove Village, IL :American Academy of Pediatrics, 1994.

Measles

Measles is a TERRIBLE disease:

- Mortality 1-3/1000 in the US (usually related to respiratory/neurologic complications)
- Pregnant women, immunosuppressed, children <5 at risk for severe disease
- Complications include pneumonia/pneumonitis, acute encephalitis (leading to permanent neurologic deficits), myocarditis/pericarditis, subacute sclerosing panencephalitis (SSPE) 7-10 years after initial infection

John E. Bennett, Raphael Dolin, Martin J. Blaser. Mandell, Douglas, and Bennett's Principles and Practice of Infectious Diseases. Philadelphia, PA :Elsevier/Saunders, 2015.

American Academy of Pediatrics. Committee on Infectious Diseases. Red Book : Report of the Committee on Infectious Diseases. Elk Grove Village, IL :American Academy of Pediatrics, 1994.

Clinical Recognition of Measles

Critically important to recognize the possibility of measles EARLY on presentation to the healthcare system and isolate the patient to prevent transmission:

- **Fever**
- **"3 Cs": Cough, Coryza, Conjunctivitis**
- **Koplik spots** may be present preceding rash and is highly associated with measles
- **Rash** – begins several days after initial symptoms appear
- *Presentation may be atypical in immunosuppressed, previously vaccinated, and infants <1 year*

John E. Bennett, Raphael Dolin, Martin J. Blaser. Mandell, Douglas, and Bennett's Principles and Practice of Infectious Diseases. Philadelphia, PA :Elsevier/Saunders, 2015.

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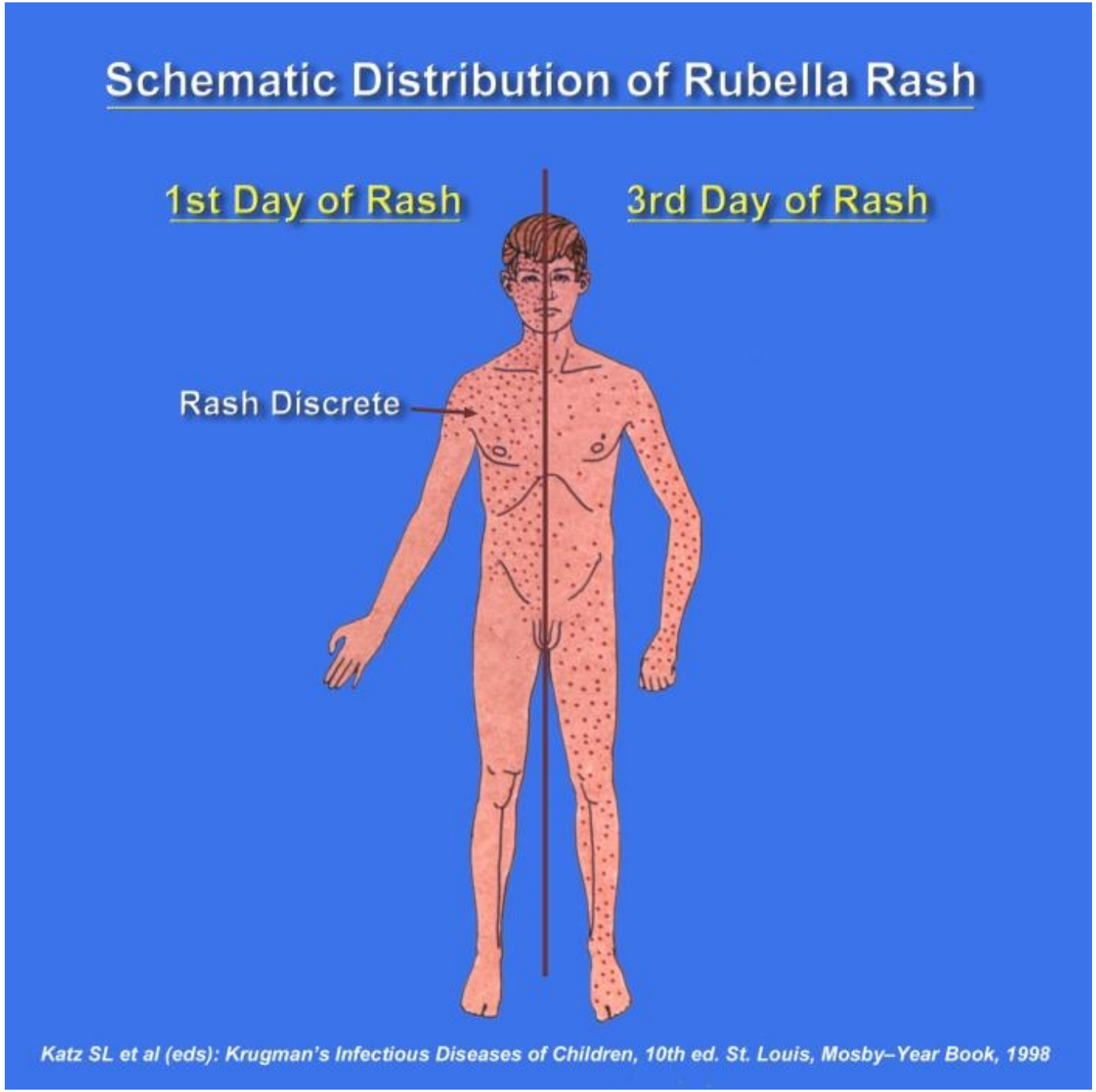
“Morbilliform”

Schematic Distribution of Rubella Rash



Katz SL et al (eds): Krugman's Infectious Diseases of Children, 10th ed. St. Louis, Mosby–Year Book, 1998

VCU Health

Conjunctivitis and Koplik Spots

Infection Control:

Airborne Isolation for suspected and confirmed cases:

- Infectious until 5 days after rash appearance (immunosuppressed for duration of illness)
- Negative Pressure
- Private room/door closed
- **N95 masks (or equivalent respiratory protection) on all providers**
- Limit visitation:
  - Remember, family is exposed – need to define vaccination status of close contacts, may be candidates for prophylaxis
  - Exposed family should stay in isolation room with patient
  - Exposed family would not be fit tested for N95 masks, and should NOT be given N95 masks – droplet masks should be used

What if there is NO negative pressure room available?

- Prioritize any existing negative pressure rooms for measles
- If no negative pressure rooms are available, keep door closed, and it must remain empty 2 hours after the patient has left the space
- Consult with the Virginia Department of Health

American Academy of Pediatrics. Committee on Infectious Diseases. Red Book : Report of the Committee on Infectious Diseases. Elk Grove Village, IL :American Academy of Pediatrics, 1994.

Post-exposure prophylaxis for Measles:

- Individuals with immunity – NO prophylaxis
- Susceptible individuals: MMR vaccine w/in 72 hours – preferred
- Susceptible immunosuppressed individuals: IVIG w/in 6 days at 400mg/kg (preferred to IMIG)

HCW should have either documentation of 2 doses of MMR vaccine or positive serology/titers

American Academy of Pediatrics. Committee on Infectious Diseases. Red Book : Report of the Committee on Infectious Diseases. Elk Grove Village, IL :American Academy of Pediatrics, 1994.

Infection Control Continued:

Management of exposed persons:

- Exposed susceptible persons must be in airborne isolation, 5-21 days after the exposure event
- Exposed susceptible HCW excluded from work 5-21 days
  - Incubation period for measles is 10-14 days
- Exposed non-susceptible HCW may continue to work while maintaining vigilance for possible symptom development

American Academy of Pediatrics. Committee on Infectious Diseases. Red Book : Report of the Committee on Infectious Diseases. Elk Grove Village, IL :American Academy of Pediatrics, 1994.

Diagnosis of Measles

***Healthcare provider MUST notify local health department of the clinical concern:**

***VDH requires all measles tests sent to Virginia Division of Consolidated Laboratory Services (DCLS)**

Ingredients of Measles Kit:

1. Serology IgM/IgG = one red/black striped top
2. Oropharyngeal (OP) swab PCR = flocked polyester fiber swab (not cotton) and universal transport medium (UTM)
2. **Nasopharyngeal (NP) swab PCR = NP swab – thin:**
3. Urine PCR = 50 ml in sterile container

DCLS Test Request Form

4 biohazard bags for specimens

1 large clear zip lock bag

Styrofoam container for transporting specimens on ice/cold pack

Ice pack zip lock or cool pack for transport

1.

2.

3.

Rubella (“German Measles”)

- Most cases of *post-natal Rubella* infections are subclinical
- If symptoms develop**, similar to a mild case of measles** (w/o the complications/sequelae)
- Post-infectious arthritis is associated, mostly in adults, 1-3 months
- **Main danger of Rubella exists to pregnant women’s developing fetuses:**
  - Miscarriage, low birth weights
  - **Congenital rubella syndrome:** variety of birth defects, some permanent, and some with developmental manifestations

John E. Bennett, Raphael Dolin, Martin J. Blaser. Mandell, Douglas, and Bennett's Principles and Practice of Infectious Diseases. Philadelphia, PA :Elsevier/Saunders, 2015.

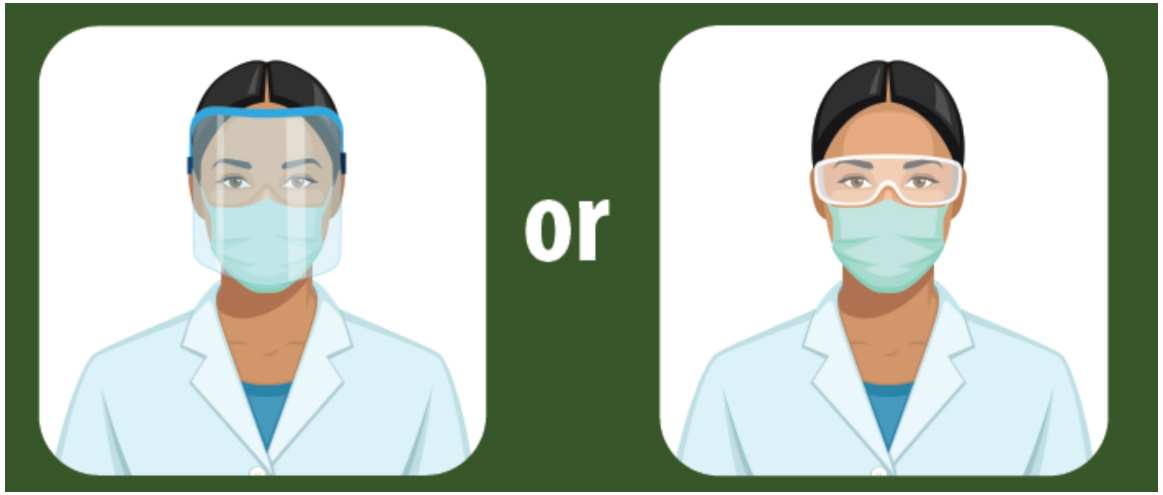
American Academy of Pediatrics. Committee on Infectious Diseases. Red Book : Report of the Committee on Infectious Diseases. Elk Grove Village, IL :American Academy of Pediatrics, 1994.

Infection Prevention: Rubella:

- Consider if you need to rule out measles
- Once measles is ruled out:

INFECTION PREVENTION:

- **Droplet Precautions**: surgical/droplet mask and eye protection
- Maintain on droplet for 7 days after onset of rash
- ***Contact isolation for infants with congenital rubella syndrome*** *until age 1 or 2 negative cultures 1 month apart and after 3 months of age*



American Academy of Pediatrics. Committee on Infectious Diseases. Red Book : Report of the Committee on Infectious Diseases. Elk Grove Village, IL :American Academy of Pediatrics, 1994.

Management of Exposed Persons:

Evidence of immunity is:

- At least 1 dose of MMR after age 1
- Positive serum IgG serology
- Born prior to 1957

It is critical to establish immunity for all HCP, especially women of child-bearing age, as there is little role for PEP in Rubella management post-exposure:

- Immune globulin IG does NOT prevent rubella infection after exposure and so is NOT recommended
- MMR can be given to those exposed w/in 72 hours based on a theoretical benefit (and that they should have it anyway), though prevention of rubella after exposure has also not been documented

American Academy of Pediatrics. Committee on Infectious Diseases. Red Book : Report of the Committee on Infectious Diseases. Elk Grove Village, IL :American Academy of Pediatrics, 1994.

Mumps

- Mostly affecting children and young adults
- Self limited/benign course, Subclinical in 1/3 of cases
- C/o HA, fever, anorexia, ear pain:
- Non-suppurative swelling and tenderness in salivary glands: most commonly parotid
- Meningitis (1-10%), transient deafness (4%), epididymo-orchitis (25% post-pubertal males), oophoritis (5% post-pubertal women) can complicate
- Less common: pancreatic involvement, migratory polyarthritis, ECG changes/myocarditis, other neurologic sequelae and hydrocephalus
- 50% will have lymphocytic pleocytosis

John E. Bennett, Raphael Dolin, Martin J. Blaser. Mandell, Douglas, and Bennett's Principles and Practice of Infectious Diseases. Philadelphia, PA :Elsevier/Saunders, 2015.

Mumps:

INFECTION CONTROL

- Droplet precautions
- Infectivity lasts until 5 days after swelling appears

Evidence of immunity is:

- Documentation of 1-2 doses of vaccine
- Positive serum IgG serology
- Born prior to 1957

MANAGEMENT OF EXPOSED HCW:

- Long incubation period: 2-4 weeks
- Exposed susceptible HCW excluded from work days 12-25 after exposure
- No benefit has been documented from post-exposure prophylaxis (so it is not done)

American Academy of Pediatrics. Committee on Infectious Diseases. Red Book : Report of the Committee on Infectious Diseases. Elk Grove Village, IL :American Academy of Pediatrics, 1994.

Diphtheria

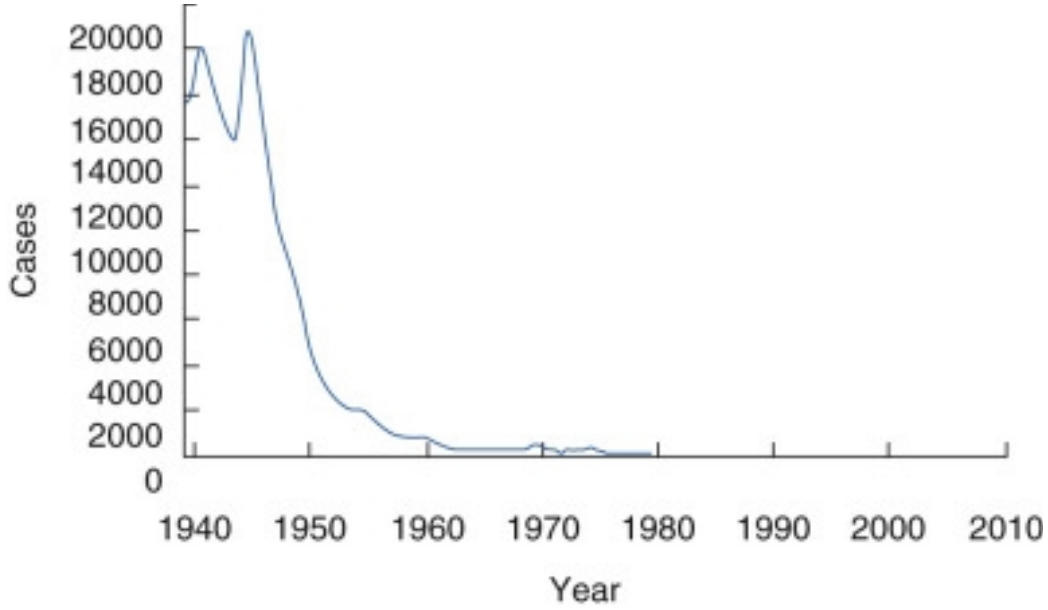
Corynebacterium diphtheriae

Corynebacterium ulcerans – produces diphtheria toxin

Today, controlled by vaccination, very sporadic cases in US

- Waning immunity in elderly persons
- Gaps in vaccine coverage by choice w/in US
- Gaps in coverage abroad for various reasons:
  - Outbreak 1990s USSR
  - Northern India

Yearly Diphtheria Cases Reported to CDC in the US:



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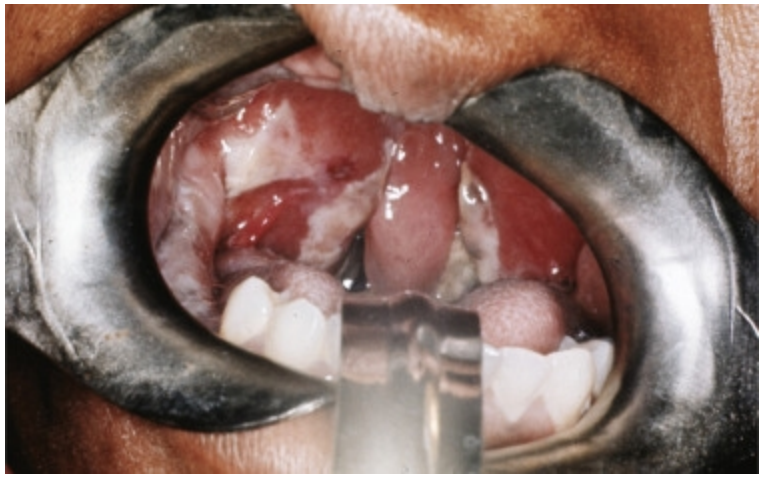
Diphtheria: Clinical Recognition



Respiratory Tract:

- **Rhinitis, Pharyngitis**
- **Cervical lymph node enlargement: "Bull Neck"**
- **Membrane can extend into larynx and trachea/bronchial tree with airway obstruction**

Cardiac Toxicity:

- ST wave changes, QT prolongation, arrhythmias, heart block, dilation

Neurologic:

- Bulbar and oculomotor paralysis can occur early
- Peripheral neuritis occurs after respiratory recovery
  - Descending motor neuropathy affecting diaphragm and limbs
  - Stocking and glove sensory neuropathy

Cutaneous Diphtheria

- Majority non-toxigenic strains – associated with poverty, ETOH, IVDU
- Can become disseminated: bacteremia, IE, septic arthritis etc

John E. Bennett, Raphael Dolin, Martin J. Blaser. Mandell, Douglas, and Bennett's Principles and Practice of Infectious Diseases. Philadelphia, PA :Elsevier/Saunders, 2015.

Diphtheria:
INFECTION CONTROL CONSIDERATIONS:

- **Transmission:** direct contact with nasopharyngeal sections OR by droplets
- **Incubation period:** 2-7 days
- **Infective period:** until off antibiotics and 2 swabs from both nose and throat are culture negative (or until about 14 days after completing antibiotics) (or 2 swabs from skin, 24 hrs apart if cutaneous diphtheria)
- **Precautions:** Droplet precautions (Contact precautions if skin lesions are present)

Management of exposed persons *regardless of vaccination status:*

(Including HCP exposed to NP secretions):

- Surveillance x 7 days for signs/symptoms
- Culture for C. diphtheria
- Erythromycin prophylaxis x 7-10 days (preferred) or single dose PCN G (1.2 million units ages 12+)
- Follow up cultures of throat after completion of therapy
  - if positive, again 10 days antibiotics

Vaccinate susceptible exposed persons and vaccinated if last booster >=5 yrs ago

NO ROLE for anti-toxin in PEP

American Academy of Pediatrics. Committee on Infectious Diseases. Red Book : Report of the Committee on Infectious Diseases. Elk Grove Village, IL :American Academy of Pediatrics, 1994.

Varicella:

Primary infection = chickenpox

- fever, malaise that can proceed a rash
- Rash: maculopapular and becomes vesicular, occurring in crops: Lesions are in various stages
- Atypical presentations in vaccinated people

Infection Control:

- **Transmission:** Spread from person to person by direct contact with rash, or via droplet or airborne spread from respiratory secretions
- **Incubation period:** 10-21 days
- **Infective period:** from 10-21 days after exposure (5 days before rash and until all lesions crusted-usually about 5 days after rash appears)
- **Precautions:** Airborne + Contact for primary varicella

American Academy of Pediatrics. Committee on Infectious Diseases. Red Book : Report of the Committee on Infectious Diseases. Elk Grove Village, IL :American Academy of Pediatrics, 1994.

Vs. Herpes Zoster

Infection Control:

- Contact precautions: until vesicular lesions are “crusted over”

Caveat:

2+ dermatomes involved: concern for **disseminated disease: use airborne/contact** precautions

American Academy of Pediatrics. Committee on Infectious Diseases. Red Book : Report of the Committee on Infectious Diseases. Elk Grove Village, IL :American Academy of Pediatrics, 1994.

Management of Exposed Persons:

Varicella vaccination, VariZIG, IVIG are used as PEP in specific circumstances:

https://www.cdc.gov/vaccines/vpd-vac/varicella/hcp-post-exposure.htm
https://www.cdc.gov/shingles/hcp/hc-settings.html

Exposure definitions for VZV:

Same household, Playmate: face-to-face indoor play, newborn infant

Hospital:

- **Varicella: Same room or adjacent beds in multi-bed ward, Face-to-face contact w/o PPE**
- Zoster: intimate contact (touching/hugging)

American Academy of Pediatrics. Committee on Infectious Diseases. Red Book : Report of the Committee on Infectious Diseases. Elk Grove Village, IL :American Academy of Pediatrics, 1994.

Tuberculosis:

- Presents as a cough for > 2 weeks with fever, night sweats, weight loss, hemoptysis
- TB incidence > 100 cases/100,000 people in Afghanistan (highest risk category)
- MDR TB a possibility – data does not exist
- Infection Control Considerations:
  - **Infective period:** Period of infectivity variable and depends on treatment and immune status
  - **Precautions:** Airborne

https://wwwnc.cdc.gov/travel/destinations/traveler/none/afghanistan

John E. Bennett, Raphael Dolin, Martin J. Blaser. Mandell, Douglas, and Bennett's Principles and Practice of Infectious Diseases. Philadelphia, PA :Elsevier/Saunders, 2015.

Pertussis: “Whooping Cough”

Several weeks of illness in 3 stages:

- 1-2 weeks of runny nose, mild fever, mild cough then:
- 2-6 weeks of increased cough with repetitive coughing spells followed by a sudden inspiration (“whoop”) with subsequent vomiting [Paroxysmal stage], then:
- ≥ 2 weeks of decreasing coughing episodes

INFECTION CONTROL CONSIDERATIONS

- **Transmission:** direct contact with nasopharyngeal sections OR by droplets
- **Incubation period:** 7-10 days
- **Infective period:** until 3 weeks after onset of paroxysmal cough OR 7 days after start of active antibiotic
- **Precautions:** Droplet

American Academy of Pediatrics. Committee on Infectious Diseases. Red Book : Report of the Committee on Infectious Diseases. Elk Grove Village, IL :American Academy of Pediatrics, 1994.

Viral Hepatitis

Hepatitis A	Abrupt onset of hepatitis with dark urine, jaundice, fever, nausea, vomiting, malaise, abdominal pain Severity increases with age	• Transmission: **Fecal-oral transmission** • Incubation period: 25-30 days • Infective period: from 7 days before to 7 days after onset of jaundice • Precautions: Contact
Hepatitis E	Fever and flu-like syndrome in about 50% followed by jaundice, nausea and right upper abdominal pain Severity increases with age **Fulminant hepatitis 30% if infected in 3rd trimester of pregnancy**	• Transmission: **Fecal-oral transmission** • Incubation period: 15-64 days • Precautions: Contact

American Academy of Pediatrics. Committee on Infectious Diseases. Red Book : Report of the Committee on Infectious Diseases. Elk Grove Village, IL :American Academy of Pediatrics, 1994.

Cholera:

- Nausea followed by massive watery diarrhea
  - **secretory infectious diarrhea**
- Life-threatening hypovolemia and electrolyte disturbance > Obtunded patients with severe cholera
- Guidelines for treatment exist:
  - LR preferred IV solution: rate 50-100cc/h
  - Oral rehydration preferred to IV for less ill and those able to take PO
  - Rehydration phase (1-4 hrs) followed by a maintenance phase(until diarrhea abates)
  - Antibiotics play a secondary role in decreasing duration of illness: doxycycline x 1 dose is first choice, alternatives exist for kids/pregnant

INFECTION CONTROL CONSIDERATIONS

- **Transmission:** Fecal-oral transmission
- **Incubation period:** a few hours to 5 days
- **Infective period:** until stool is culture negative (usually a few days after recovery or antibiotic therapy); carrier states may lead to shedding in stool for months
- **Precautions:** Contact

American Academy of Pediatrics. Committee on Infectious Diseases. Red Book : Report of the Committee on Infectious Diseases. Elk Grove Village, IL :American Academy of Pediatrics, 1994.

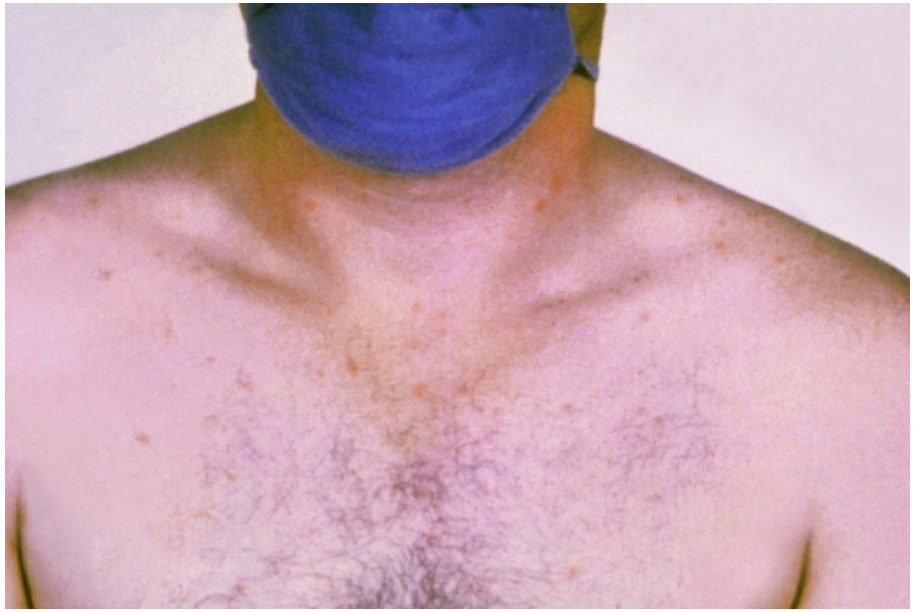
Typhoid Fever/Enteric Fever

Salmonella typhi and *Salmonella paratyphi*

- Can be insidious at onset: fever, abdominal pain
- Possible rash and relative bradycardia
- Transmitted via contaminated food and water, person to person uncommon
  - water: less bioburden>longer incubation and lower attack rate
- Outbreaks involving HCW in setting of suboptimal HH
- 1-4% may develop chronic carrier state, requiring 4-6 weeks antibiotics to erradicate
- Antibiotic therapy: quinolones, azithromycin, ceftriaxone

American Academy of Pediatrics. Committee on Infectious Diseases. Red Book : Report of the Committee on Infectious Diseases. Elk Grove Village, IL :American Academy of Pediatrics, 1994.

- **Transmission:** Fecal-oral transmission
- **Incubation period:**
  - Typhoid: 3-31 days
  - Paratyphoid: 1-60 days
- **Infective period:** for duration of diarrhea
- **Precautions:** Contact



Rose Spots

Polio

- Wild type and vaccine-derived circulating throughout Afghanistan as of March 2020
- Many asymptomatic, non-specific symptoms of fever, sore throat, gastroenteritis, 1/1000 will have frank paralysis
- Large muscle groups, motor, autonomic (NO sensory)
- Diagnosis: PCR in stool or CSF (low yield CSF), acute and convalescent sera
- Transmission: respiratory secretions and fecal-oral
- Incubation period: 3-35 days
- Infective period: until stools negative OR 7 days from illness onset, droplet spread possible during that first week
- Precautions: Contact
- Treatment: supportive

John E. Bennett, Raphael Dolin, Martin J. Blaser. Mandell, Douglas, and Bennett's Principles and Practice of Infectious Diseases. Philadelphia, PA :Elsevier/Saunders, 2015.

https://wwwnc.cdc.gov/travel/destinations/traveler/none/afghanistan

Rabies:

- Exposure to saliva from an infected animal (mammal), usually in the form of a bite.
- Clinical illness can begin after a variable incubation period: weeks to several months
- Pain and paresthesia at sight often first symptoms – overlooked
- This is followed by non-specific prodromal febrile illness, followed by acute/progressive and invariably fatal encephalitis

“Rabid dogs are commonly found in Afghanistan. If you are bitten or scratched by a dog or other mammal while in Afghanistan, there may be limited or no rabies treatment available.”

https://wwwnc.cdc.gov/travel/destinations/traveler/none/afghanistan

American Academy of Pediatrics. Committee on Infectious Diseases. Red Book : Report of the Committee on Infectious Diseases. Elk Grove Village, IL :American Academy of Pediatrics, 1994.

Case Study: Virginia, 2017:

- 65 y/o woman with no PMHx began experiencing pain/paresthesia in her RUE while gardening. 3 days later, she went to urgent care for this issue, and was diagnosed Carpal tunnel syndrome, given NSAIDS.
- A day later she went to local ER with SOB, anxiety, insomnia, and difficulty swallowing. She was c/f exposure to a toxin of some kind. However, objectively, ER finds nothing and send home with Ativan for presumed panic attacks.
- Next day, EMS called and takes her to another ER for SOB, chest pain, and progressive paresthesia of R shoulder and arm, increased anxiety. This time exam notable for dysmetria, and cardiac enzymes elevated along with ECG suggestive of NSTEMI- getting her a LHC – normal. Admitted however, and later that evening becoming progressively agitated/combative, was noted by staff to be gasping for air when attempting to drink.
- Eventually, providers learn that 6 weeks ago on travel to India, she had been petting a puppy outside the hotel and it bit her. She washed the wound with tour operator, but no other care sought.
- >200 HCW assessed for exposure, PEP provided to 72 HCW that met definition, cost >$235,000

Murphy J, Sifri CD, Pruitt R, et al. Human Rabies — Virginia, 2017. MMWR Morb Mortal Wkly Rep 2019;67:1410–1414.
DOI: http://dx.doi.org/10.15585/mmwr.mm675152a2external icon.

TABLE 1. Antemortem diagnostic testing* of specimens in a case of human rabies transmitted by a dog bite received in India — Virginia, 2017

Specimen type	Testing method	Date specimen collected							
		May 9	May 12	May 14	May 15	May 16	May 17	May 18	May 19
CSF	IFA IgG	Neg	—	Neg	—	—	Neg	Neg	—
	IFA IgM	Neg	—	Neg	—	—	Neg	Neg	—
	RFFIT	Neg	—	Neg	—	—	Neg	Neg	—
Serum	IFA IgG	Neg	Neg	—	Neg	Neg	Neg	—	—
	IFA IgM	Neg	Neg	—	Neg	Neg	Neg	—	—
	RFFIT	Neg	Neg	—	Neg	Neg	Neg	—	—
Saliva	Isolation in MNA	Neg	—	—	—	Pos	Pos	Pos	Pos
	real-time RT-PCR†	Pos	Pos	Pos	Pos	Pos	Pos	Pos	Pos
Skin biopsy	DFA	Pos	—	—	—	—	—	—	—
	real-time RT-PCR†	Pos	—	—	—	—	—	—	—

Abbreviations: CSF = cerebrospinal fluid; DFA = direct fluorescent antibody; IFA = indirect fluorescent antibody; IgG = immunoglobulin G; IgM = immunoglobulin M; MNA = mouse neuroblastoma cell culture; Neg = negative; Pos = positive; RFFIT = rapid fluorescent foci inhibition test; RT-PCR = reverse transcription–polymerase chain reaction.

* Positive result indicates detection of rabies virus antigen; negative result indicates no detection of antibody to rabies virus.

† RT-PCR conducted in triplicate.

Murphy J, Sifri CD, Pruitt R, et al. Human Rabies — Virginia, 2017. MMWR Morb Mortal Wkly Rep 2019;67:1410–1414. DOI: http://dx.doi.org/10.15585/mmwr.mm675152a2external icon.

Questions?