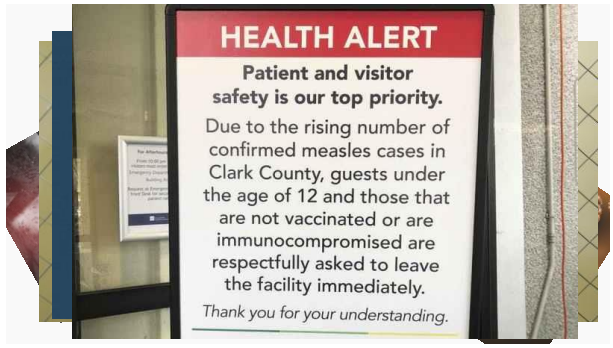
The Measles Outbreaks: Have we lost our elimination status?

Clinical Laboratory Personnel Committee (CLPC)
Fall 2019



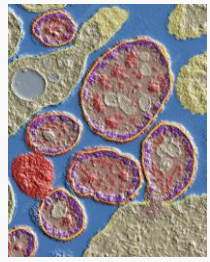
Objectives

1. Describe measles infection in terms of: etiologic virus, immune response, clinical presentation, prognosis, and prevention.
2. Explain the laboratory methods used to diagnose and monitor measles infections.
3. Discuss the current measles outbreak worldwide and in the U.S.

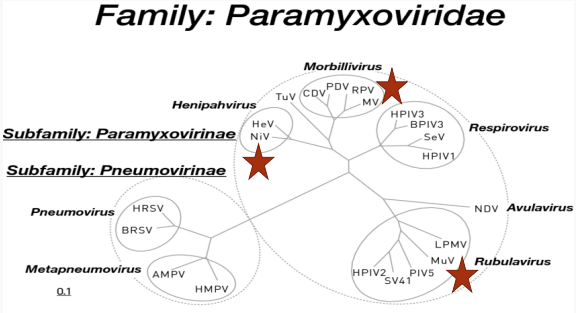
The Measles virus

Rubeola virus

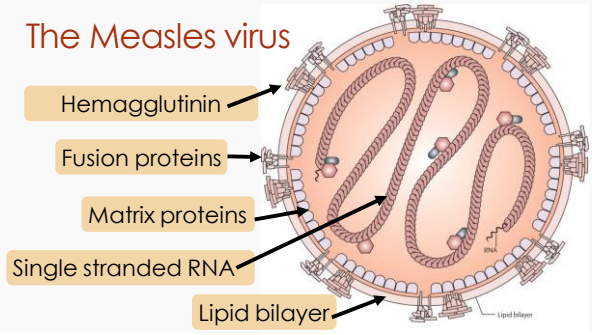
- Family: Paramyxoviridae
  - Genus: Morbillivirus
- Affinity for mucous membranes
- Greek: myxa = mucus

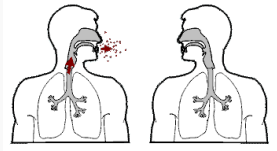


Measles virus particles in culture, TEM
Photo credit: Eye of Science/ Science Photo Library



The Measles virus

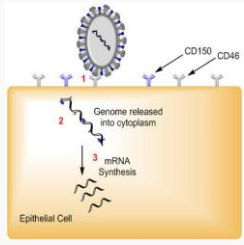




Viral transmission

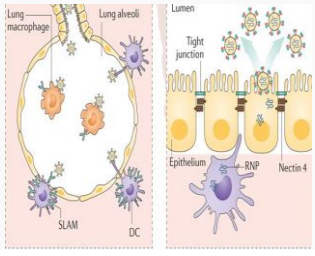
- Highly contagious
- Respiratory droplets
- Direct contact
- Contaminated surfaces
- Viable for 2 hours

Immunopathology of measles

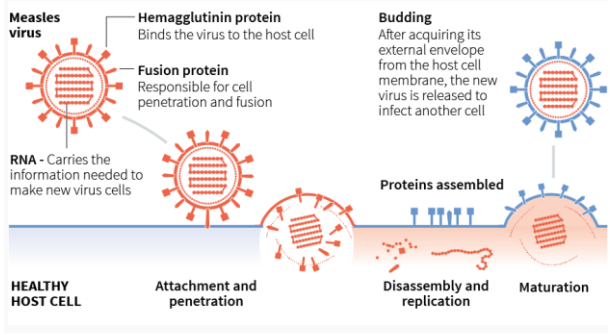


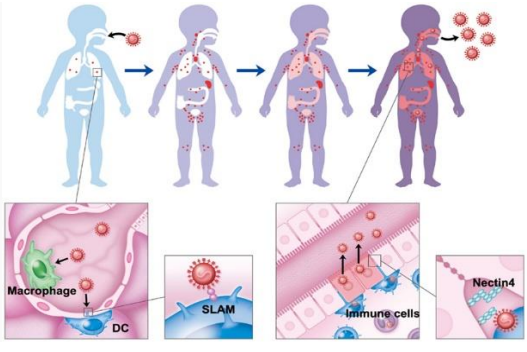
- Invasion of cells lining upper respiratory tract
- Systemic manifestations
- Using H and F proteins
- Cell receptors:
  - CD46
  - CD150 (SLAM)
  - Nectin-4

Immunopathology of measles



- Invades epithelial cells
- Invades alveolar macrophages
- Uptake by dendritic cells (DCs)
- DCs transport to lymph nodes
- Continued replication in reticuloendothelial system
- **Primary viremia**
- Viral exit from epithelials
- 10 – 14 day incubation





Characteristic symptoms of measles

Prodromal
Cold sx
Conjunctivitis
Lasts 2-4 days

Koplik spots
During prodromal period
Persist for several days

Rash
14 days after exposure
Starts at hairline
Lasts 5-6 days

Prodromal period

3 C's and 4 D's

COUGH	CORYZA	CONJUNCTIVITIS	FEVER
• Dry • Persistent • Sore throat	• Runny nose • Sneezing	• Red, watery eyes • Pink eye	• Very high up to 104° F

Koplick spots

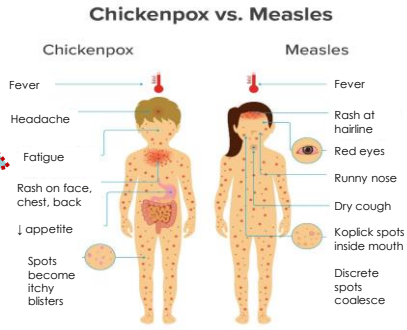
- Henry Koplick (1858 – 1957)
- **Pathgnomonic for measles**
- Appear during prodromal period
- Remain for several days
- Fade away as rash comes on
- White lesions on buccal mucosa
- Opposite 1st and 2nd molars
- "grains of salt on red background"

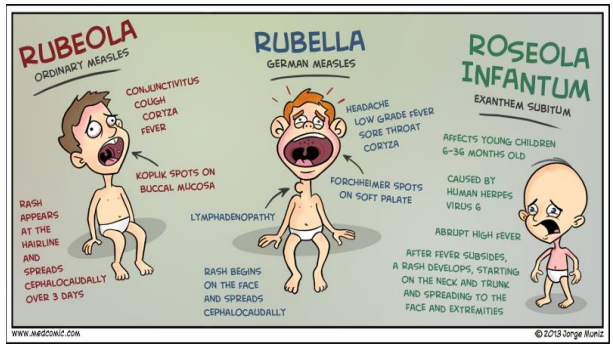
Measles rash

- Appears about 2 – 6 days after cough
- Maculopapular, erythematous
- Type IV hypersensitivity
  - *CD8+ T-cells attack viral-infected endothelial cells in skin*
- Begins at hairline or behind ears
- Red macules that blanch with pressure
- Within 12 – 24 hours, macules become papules that coalesce

Measles rash

- Progresses from head to trunk to extremities
- Hands and feet may be spared
- Fades in same head-to-toe fashion
- Coppery brown patches
- May be itchy
- May peel as it fades
- Lasts 5 – 6 days

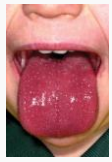




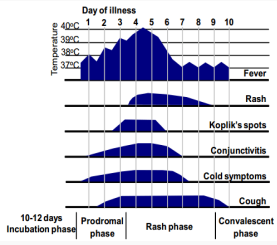
NAME THAT RASH!

MEASLES

SCARLET FEVER



Clinical picture of Measles



- Symptoms begin 10 – 14 days after exposure
- DAY 1: low fever, runny nose
- DAY 2: cough, conjunctivitis
- DAY 3: Koplick spots appear
- DAY 4: high fever, rash begins
- DAY 5: rash spreads downward
- DAY 6: fever and cold sx decrease
- DAY 7 – 10: rash, cough, fever resolve

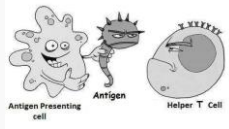
Prognosis

- Generally good
- U.S. mortality rate 0.1% - 0.2%
- Case fatality highest in ages 4-12 mths
- Morbidity/mortality increased in immunocompromised
  - HIV
  - Malnourished
  - Vitamin A deficiency
  - Inadequate vaccination
  - < 5 years old

Immunosuppression from measles

- Generalized systemic immunosuppression
- ↓ interleukin-12 (IL-12) production
- ↓ antigen-specific lymphoproliferative responses
- May persist for weeks – months after acute infection

- Reactivation of latent infections
- Secondary infections



Severe Complications of measles

- Secondary opportunistic infections:
  - Otitis media
  - Bronchopneumonia
  - Laryngotracheobronchitis (croup)
  - Tuberculosis
  - Sinusitis
  - Keratitis --- blindness
- Hepatosplenomegaly and hepatitis
- Encephalitis
- Subacute sclerosing panencephalitis (SSPE)

Measles encephalitis

- 1 of every 1,000 patients
- Permanent brain damage
- Fatal in 10% of patients

- Delayed-acute measles encephalitis may develop 1 – 6 months after acute infection

Subacute sclerosing panencephalitis (SSPE)

- Very rare complication of measles
- Degenerative CNS disease
- Results from persistent measles infection
- Onset years after acute infection (mean: 10.8 years)
- Behavioral and intellectual deterioration
- Seizures

Measles in the pregnant mother

- Perinatal transmission rates are low
- Complications to pregnancy outcomes:
  - Hepatitis
  - Pneumonitis
  - SSPE
  - Premature labor
  - Spontaneous abortion
  - Preterm birth

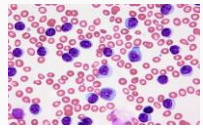
Diagnosis

- Clinical presentation
- Patient history
- Vaccine history
- Laboratory confirmation for public health surveillance
  - Complete blood count (CBC)
  - Liver function test
  - Viral cell culture
  - Antibody testing
  - Molecular testing

Laboratory confirmation

CBC

- Leukopenia
- Relative lymphocytosis
- Thrombocytopenia



LIVER FUNCTION

- Elevated liver enzymes (AST, ALT, ALP)

Multinucleate giant cells

- Detectable in nasopharyngeal secretions during prodromal period
- Can also be seen in viral culture
- Syncytia: ≥ 50 nuclei within single cytoplasm

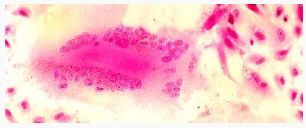
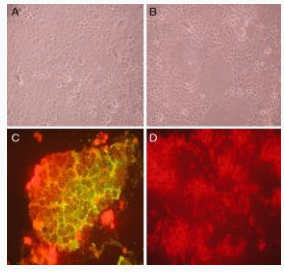


Photo courtesy of Linda Stannard, University of Capetown, S.A.

Viral cell culture



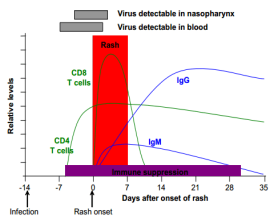
A. Control cell culture

B. Infected multinucleate cells (throat swabs)

C. Immunofluorescence of viral infected cells

D. No fluorescence in control cells

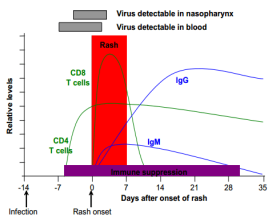
Antibody serology



IgM assay

- Indicates current infection
- Sandwich-capture ELISA
- Detectable on/after 3rd day of rash
- May remain positive 30-60 days after rash onset
- False positives: rheumatologic disease, parvovirus B19, infectious mononucleosis

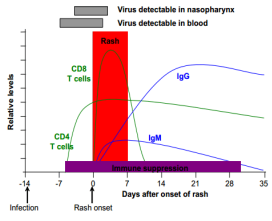
Antibody serology



IgG assay

- ≥ 4-fold rise in titer between acute and convalescent sera
- Detectable 4-7 days after rash onset
- Collect acute sera on day 7
- Collect convalescent sera 10-14 days later
- Test as paired sera to observe rise in titer

Molecular testing



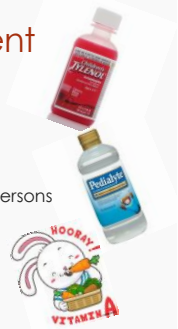
Reverse-transcription PCR

- Highly sensitive
- Detects viral RNA
- Sample can be blood, throat swab, NP swab, or urine
- Should be collected at first contact of suspected case

Treatment & Management

- Supportive care with good hydration
- Antipyretics for fever management
- Vitamin A supplementation
- Antibiotics for secondary bacterial infections
- Post-exposure prophylaxis in unvaccinated persons
- Regular follow-up care with PCP

- Airborne precautions in hospitalized children



Prevention = Vaccination

- MMR or MMRV
- Infants and children
- 1st dose at 12-15 months
- 2nd dose at 4-6 years

- Live attenuated
- Induces active immunity

- Contraindicated during pregnancy

History of measles disease

9th century	• First written account, Persia
1757	• Francis Home, Scotland • Demonstrated that measles caused by infectious blood
1912	• Became nationally notifiable disease in U.S. • Average of 6,000 cases reported per year
1953 - 1963	• Nearly all kids infected by age 15 • Estimated 3 – 4 million infected each year • 48,000 hospitalized

Vaccine development

1954 – Enders and Peebles, Boston Children's Hosp.

- Outbreak at private school
- "Young man, you are standing on the frontiers of science."
- Virus isolated from 13 y.o. David Edmonston

1958 – first version of vaccine tested

- 11 children vaccinated
- All developed antibodies
- 9 developed mild rash

1960 – additional testing in NY school

- 23 children vaccinated
- Protected from outbreak 6 weeks later

Vaccine development

1962 – Hilleman creates successful version

- Passed Enders strain through 80 cell lines
- Rubeovax given with gamma globulin

1963 – first licensed vaccine, Edmonston-B strain

1968 – Hilleman more attenuated version

- Passed virus through chick embryo cells 40 times
- Moraten strain (*Mo*re *At*tenuated *En*ders)

1971 – MMR combo licensed

- 96% effective against measles, 95% against mumps, 94% against rubella

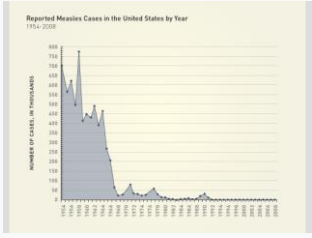
Vaccine development

1978 – CDC goal to eliminate from U.S.

- Measles Elimination Program
- Eliminate by 1982

1989 – ACIP recommendation for 2nd booster dose for all children

- Major outbreaks due to low vaccination
- 55,622 sick, 123 died
- 90% of fatalities were never vaccinated



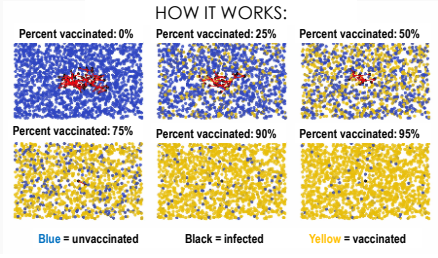
Vaccine development

1998 – Andrew Wakefield scandal

- Completely unfounded and unethical
- All findings retracted in 2004
- Wakefield convicted of gross misconduct in 2010
- Banned from practicing medicine in Britain

- THERE IS NO LINK BETWEEN MMR VACCINE AND AUTISM!

Maintaining **Herd Immunity**



Measles declared eliminated!!!

- Eliminated: absence of continuous disease transmission for greater than 12 months
- **Endemic measles** eliminated from U.S. in 2000
- Highly effective vaccine programs
- Disease control in Americas region
- Americans still at **risk for imported cases**

- Endemic measles eliminated from Americas in 2016

Worldwide Outbreaks

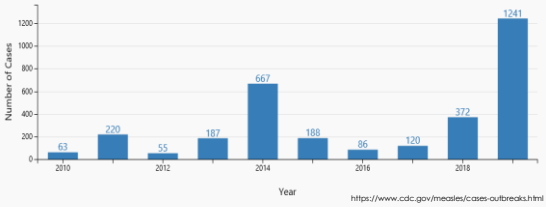
World Health Organization (WHO) reports:

- Estimated 7 million people affected in 2016
- 110,000 deaths in 2017, mostly kids < 5 years old
- Low immunization rates <95%
- Ukraine, Israel, Italy, Romania, France, Venezuela, Bulgaria, Philippines….

- Policy changes: fines and mandatory vaccination

United States Outbreaks

Number of Measles Cases Reported by Year
2010 – 2019 (as of September 12, 2019)



2015, Disneyland, CA

- Anaheim, California
- Unidentified source
- 111 cases from Disneyland
- 188 total for the year 2015

United States Outbreaks

2016	2017
ICE detention center, AZ 31 total cases Median detainee age: 34 Median staff age: 41	Minnesota Somali-American community 75 cases Median patient age: 21 mths 95% of affected children were unvaccinated

United States Outbreaks, 2018

- 17 outbreaks
- Majority of cases from New York and New Jersey
- Unvaccinated people in Orthodox Jewish communites
- Imported from travel to Israel

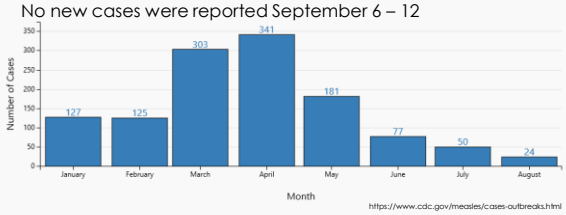
- Greatest number of imported cases since 2000

Most recent CDC update

Measles cases in 2019

From January 1 to September 12, 1241 cases reported in 31 states

No new cases were reported September 6 – 12



https://www.cdc.gov/measles/cases-outbreaks.html

Measles cases in 2019

- Greatest number of reported cases since 1992
- >75% of cases are linked to outbreaks in New York
- Majority of cases among unvaccinated people
- 130 hospitalizations
- 65 reported complications of pneumonia and encephalitis

https://www.cdc.gov/measles/cases-outbreaks.html

States with reported measles cases in 2019

Alaska
Arizona
California
Colorado
Connecticut
Florida
Georgia
Hawaii
Idaho
Illinois
Indiana
Iowa
Kentucky
Maine
Maryland
Massachusetts
Michigan
Missouri
New Mexico
Nevada
New Hampshire
New Jersey
New York
Ohio
Oklahoma
Oregon
Pennsylvania
Texas
Tennessee
Virginia
Washington

Ongoing outbreaks at this time

1.NY state, Rockland County

2.NY state, Wyoming County

- Travelers from Israel, Ukraine, and Philippines

Have we lost our elimination status?

- U.S. resident traveled to Israel
- Under-vaccinated community
- >400 cases in this outbreak
- Peaked in November 2018
- Peaked in March/April 2019

Maintaining measles elimination status

- Historic public health achievement
- Overall vaccine coverage remains high in the U.S.
- No economic, political, or practical penalties for losing elimination status
- Maintaining elimination status

Questions and Discussion

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