Paramyxoviruses

Reading: Schaechter's Mechanisms of Microbial Disease, 4th edition, 2007, Engleberg, DiRita & Dermody. Chapter 34

I. General characteristics
   A. Classification: Order *Mononegavirales*
      1. Families *Rhabdoviridae*, *Filoviridae* and *Paramyxoviridae* all similar in genetic organization and replication
      2. Family *Paramyxoviridae*
         a. Subfamily *Paramyxovirinae*
            i. *Rubulavirus* (Mumps, Parainfluenzavirus 2,4)
            ii. *Respirovirus* (Parainfluenzavirus 1,3)
            iii. *Henipavirus* (Hendra, Nipah) (rare, emerging zoonosis)
            iv. *Morbillivirus* (Measles)
         b. Subfamily Pneumovirinae
            i. *Pneumovirus* (Respiratory syncytial virus)
            ii. *Metapneumovirus* (Human metapneumovirus)
   B. Virion structure
      1. Enveloped virus
      2. Single stranded, negative (-) sense RNA
      3. Helical nucleocapsid: nucleocapsid protein (N)
      4. RNA-dependent RNA polymerase - P and L protein subunits
      5. Matrix protein (M)
      6. Envelope glycoproteins (HN/H/G)
         a. Hemagglutinin-neuraminidase (HN) in mumps and PIV
         b. Hemagglutinin (H) only in measles
         c. Glycoprotein (G) in RSV ,hMPV; no hemagglutinin or neuraminidase activity
         d. All used for virus attachment
      7. Envelope fusion protein (F)
         a. Used for fusion and entry
   C. Genome structure
      1. 10-15 kb single stranded, negative (-) sense RNA
      2. Encodes 6 (paramyxoviridae) or 5 (rhabdoviridae) proteins
      3. HN = mumps, PIV; H = measles; G = RSV ,hMPV, rabies
      4. Rabies lacks F
      5. P encodes 2-3 proteins in Paramyxovirinae (P/V/C)
      6. Rubula-, Pneumo-, and Metapneumo- contain extra genes (M2, SH)
      7. F & G switched in Pneumoviruses
   D. Virus replication
      1. Entirely cytoplasmic
      2. Attachment by HN/H/G protein to cells - neutralizing antibody is directed against HN/H/G
      3. Fusion of viral envelope with cell membrane via F protein results in entry
         a. Fusion results in giant cell formation (syncytia)

b. Antibody to F to prevents spread of virus from cell to cell
4. Virion RNA polymerase directed viral mRNA synthesis
5. Full length (+) sense anti-genome synthesis and genome replication
6. Assembly and budding

II. Measles
A. One of the five classical childhood exanthems (eruptive diseases) which include rubella (togavirus), roseola (HHV 6), chickenpox (herpes zoster) and fifth disease (parvovirus, B19, erythema infectiosum).
B. One of the most prominent causes of disease (30-40 million cases per year) and death (1-2 million per year) in unvaccinated populations
C. Fewer than 1000 cases in US since 1993; result of live vaccine
D. Host range limited to humans, one serotype
E. Pathogenesis
1. Respiratory transmission; extremely contagious
2. Contagion during prodrome (5-9 days)
a. sore throat, malaise, fever
3. Specific symptoms
a. CCC&P: cough, coryza, conjunctivitis & photophobia
b. Koplik spots - red with white centers on inside of mouth
4. Spread
a. Replication in lymph nodes
b. Cell associated viremia
c. Widespread dissemination
i. Conjunctivae
ii. Respiratory tract
iii. Urinary tract
iv. Small blood vessels
v. Lymphatic system
vi. CNS
5. Maculopapular rash
a. Duration14 days
b. Spreads from forehead down trunk and out extremities
c. Caused by replication of virus in skin; most symptoms result from immune response to infection (T cell deficient patients have no rash)
6. Rarely an inapparent infection
7. More severe in adults than children.
8. Recovery in most cases
a. Lifelong immunity
F. Complications
1. Viral or bacterial pneumonia
2. Atypical measles
a. Immune sensitization due to an early inactivated viral vaccine (1963-67) or (rarely) attenuated vaccine; enhanced immunopathology
3. Acute post-infectious encephalitis (or ADEM- acute disseminated encephalomyelitis); 5-7 days after rash; demyelinating autoimmune disease

4. SSPE - subacute sclerosing panencephalitis, years after infection, mutant virus, lethal persistent brain infection.
5. Unresolved infection in immune compromise

G. Diagnosis
1. Clinical manifestations: Koplik's spots, maculopapular rash, fever, CCC&P
2. Virus culture (difficult)
3. Serology for antibody
4. rtPCR
5. Immunofluorescence for measles antigen

H. Vaccine.
1. Live attenuated vaccine in MMR; injected
   a. One serotype
   b. Timing with respect to maternal immunity a consideration
   c. Antibody response good, but not lifelong as in natural infection.
      i. Revaccinate at 18-20 yrs
   d. Recent outbreaks due to unvaccinated individuals

III. Mumps

A. Host range limited to humans, one serotype

B. Pathogenesis
1. Respiratory transmission
   a. Less contagious than measles
2. Prodrome: sore throat, cough
   a. Contagion period precedes symptoms.
3. Spread
   a. Replication in lymph nodes
   b. Viremia
   c. Primary target organ is parotid (salivary) gland at 18-21 days
4. Symptoms
   a. Parotid gland swelling due to edema and local inflammatory response
   b. 10% not bilateral, some have no swelling at all.
   c. Also causes swelling in testes, ovaries. Can cause sterility in males
   d. 30% inapparent infections
5. CNS complications: aseptic meningitis, but full recovery, rarely encephalitis

C. Diagnosis
1. Clinical
2. Serology
3. Culture
4. Hemadsorption

D. Vaccination
1. Live attenuated vaccine in MMR; injected
2. One serotype
3. 80% effective with one dose, 90% effective with two doses

E. Recent outbreaks
1. 2006: 6584 cases in Midwestern US mostly in vaccinated college students in dormitories
2. 2006-2009: return to normal levels (100-200/yr)

3. 2009: 1521 cases in New York & New Jersey in a summer camp for tradition-observant Jewish boys, mostly vaccinated
4. Occurred in congregate settings, where prolonged, close contact among persons might be facilitating transmission
5. In cases, index cases were imported from UK where vaccination rates have recently been low resulting in epidemic mumps

IV. Vaccines and autism
- A. 1998: a British gastroenterologist, Andrew Wakefield, M.D. authors Lancet article suggesting that the measles, mumps, and rubella (MMR) vaccine might cause symptoms associated with autism
  1. Case study of eight children who had received the MMR and then developed symptoms of autism
- B. Eighteen subsequent controlled epidemiological studies find no link between MMR or thimerosal (preservative) and autism
- C. 2004: Institute of Medicine concluded: "the body of epidemiological evidence favors rejection of a causal relationship" between both the MMR vaccine and thimerosal, and autism
- D. 2004: 10 of the 13 authors of the Wakefield study retracted it
- E. February 2010: The Lancet retracted Wakefield's entire study after an independent government review concluded that he had acted "dishonestly and irresponsibly" in conducting his research.
- F. May 2010, Wakefield banned from practicing medicine in the UK.

V. Respiratory syncytial virus
- A. Widespread: 75% of infants seropositive by 1 year of age
- B. Yearly in US 50,000-80,000 hospitalizations, 100 infant deaths, 17,000 elderly deaths
  1. Most common cause of fatal acute respiratory tract infections in infants and young children
- C. Host range limited to humans; single serotype
- D. Respiratory transmission
  1. Aerosol droplets or fomites, hand to nose contact, usually in the winter months
  2. Highly contagious; contagion period precedes symptoms and may occur in absence of symptoms
- E. Localized infections of respiratory tract, no viremia and no systemic infections
- F. Disease
  1. Children < 1 y.o.: bronchiolitis
     a. Wheezing, dyspnea, air trapping, hyperexpansion of lung, decreased ventilation; resembles asthma
     b. Caused by host immune response, particularly severe in infants, resembles asthma and blocks airways. Unusual in that severe infection occurs in first year in the face of maternal antibody. Also causes pneumonia
  2. Pneumonia
  3. Common cold in older children and adults
- G. Poor immunity
  1. Reinfection occurs throughout life

2. Maternal antibody does not prevent infection

H. Diagnosis
   1. rtPCR, immunofluorescence, enzyme immunoassay, serology
   2. Culture difficult

I. Treatment
   1. Ribavarin reduces severity of symptoms in immunocompromised patients

J. No vaccine; improper vaccination increases severity of disease

K. Passive vaccination for high risk infants
   1. Palivizumab: anti-F monoclonal antibody

VI. Parainfluenza viruses

A. Four serotypes, host range limited to humans,

B. Respiratory transmission

C. Infections limited to respiratory tract, generally non-systemic and viremia rare.

D. Causes cold-like symptoms, bronchitis and croup (serotypes 1 and 2). Infections of children common.

E. Diagnosis
   1. Virus culture
   2. Syncytia formation
   3. Hemadsorption
   4. Hemagglutination inhibition
   5. rtPCR

F. Immunity following infection short-lived. Individuals subject to re-infection.

G. Candidate vaccines are in various stages of clinical trials.

VII. Human metapneumoviruses

A. Newly discovered

B. Respiratory transmission

C. Disease: asymptomatic, common cold, bronchiolitis, pneumonia
   1. Accounts for 15% of common colds in children

D. Diagnosis by rtPCR

Paramyxoviruses

Measles, mumps, parainfluenza virus, respiratory syncytial virus, human metapneumovirus

Case presentation

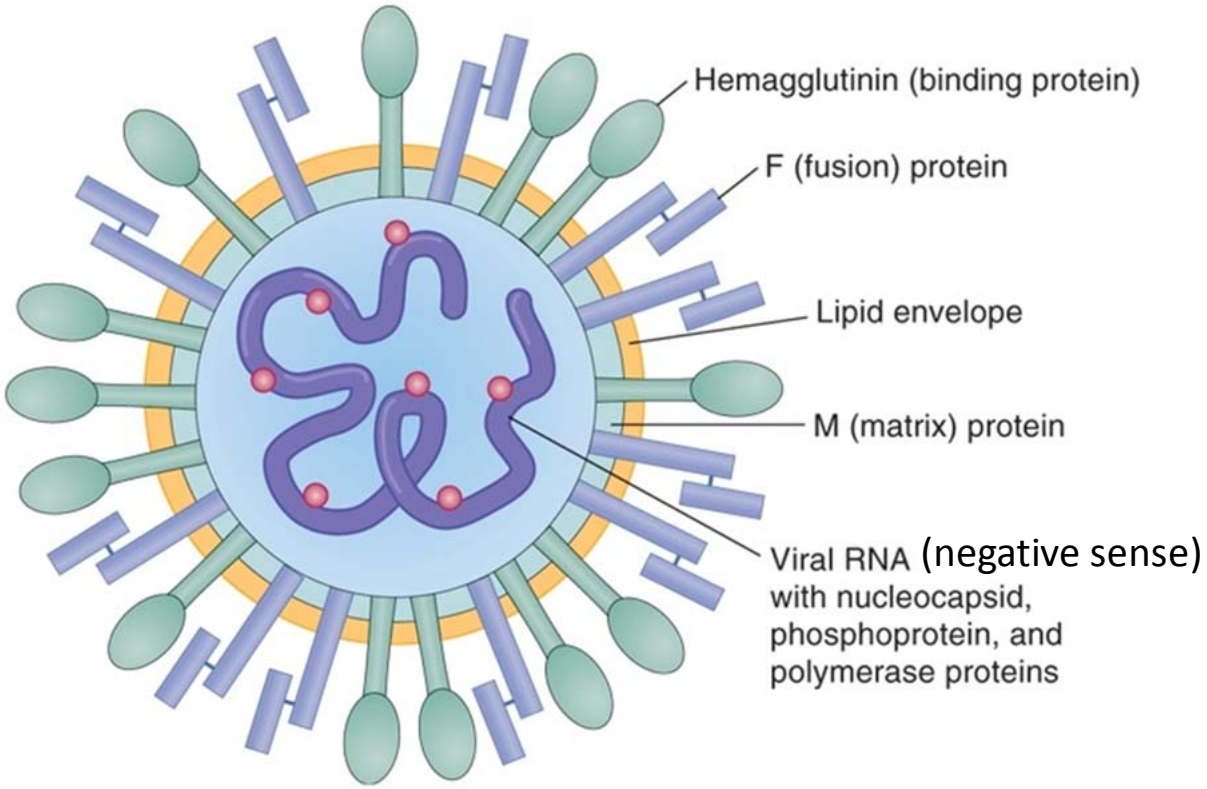
The patient was a 9 year old female who was brought to her pediatrician in February because of fever and rash for 2 days. She also had a headache, sore throat, and mild cough. There were no gastrointestinal symptoms. No one else in the household was ill, but she had a classmate with similar illness.

On examination she was alert and in mild distress. Her temperature was 38.3^{o}C, pulse rate was 110 beats/min, blood pressure was 90/60 mmHg, and respiratory rate was 40/min. She had a mild conjunctivitis. Her posterior pharynx was injected, and petechiae were present on her soft palate. The buccal mucosa was injected with scattered raised papular lesions. She had a macular rash on her trunk, face and arms. Her chest radiograph was normal. A throat swab was sent for culture and blood was drawn for viral serologic examination. Subsequently, the throat culture was read as negative for group A beta-hemolytic streptococci. Acute and convalescent phase (obtained 2 weeks later) serum specimens confirmed the clinical diagnosis of measles, and the school nurse was notified.

Human pathogens in the order *Mononegavirales*

Family	**Subfamily**	**Genus**	**Human pathogens**
Rhabdoviridae			
		Lyssavirus	Rabies virus
Filoviridae			
		Marburghvirus	Marburgh virus
		Ebolavirus	Ebola virus
Paramyxoviridae			
	Paramyxovirinae		
		Rubulavirus	Mumps virus, Parainfluenzavirus 2,4
		Respirovirus	Parainfluenza virus 1,3
		Henipavirus	Hendra virus, Nipah virus
		Morbillivirus	Measles virus
	Pneumovirinae		
		Pneumovirus	Respiratory syncytial virus
		Metaneumovirus	Human metapneumovirus

Paramyxoviridae structure

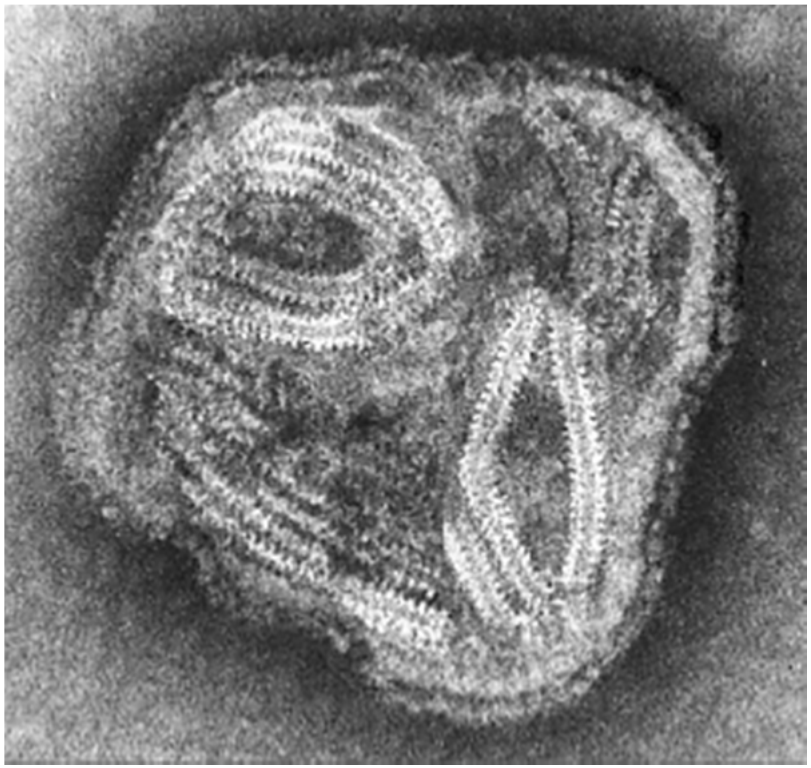


From Schaechter's Mechanisms of Microbial Disease; 4th ed.; Engleberg, DiRita & Dermody; Lippincott, Williams & Wilkins; 2007; Fig. 34-1

HN/H/G:

- Hemagglutinin-neuraminidase (HN) in mumps and PIV
- Hemagglutinin (H) only in measles
- Glycoprotein (G) in RSV ,hMPV; no hemagglutinin or neuraminidase activity

Paramyxovirus structure

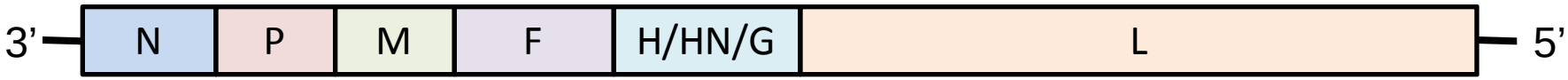


Paramyxovirus electron micrograph

http://web.uct.ac.za/depts/mmi/stannard/paramyx.html

Mononegavirales genome structure

Paramyxoviridae



Rhabdoviridae

10-15 kb in size

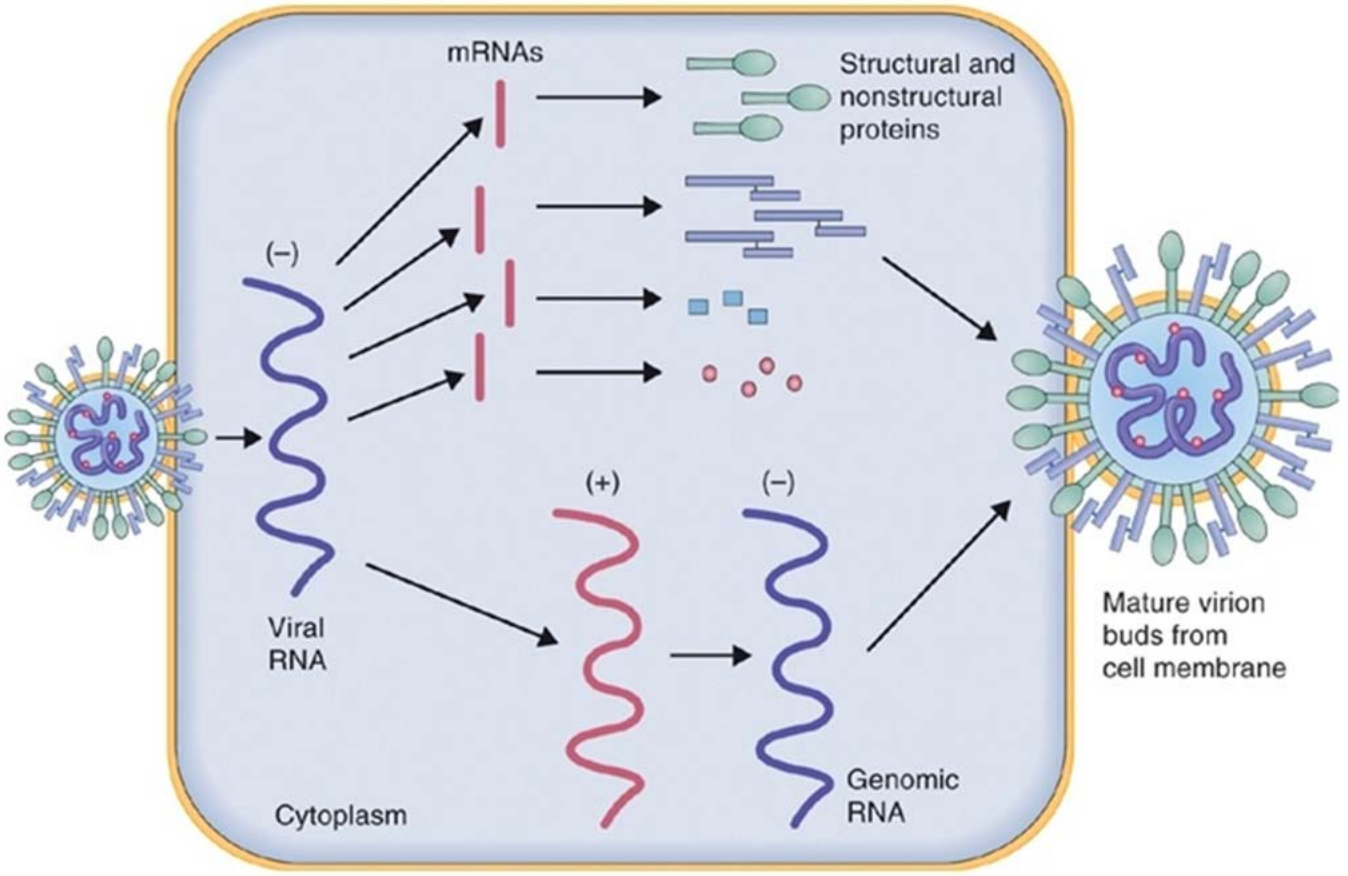
Notes:

1) HN = mumps, PIV; H = measles; G = RSV ,hMPV, rabies
2) Rabies lacks F
3) P encodes 2-3 proteins in *Paramyxovirinae* (P/V/C)
4) *Rubula-*, *Pneumo-*, and *Metapneumo-* contain extra genes (M2, SH)
5) F & G switched in *Pneumoviruses*

Mononegavirales gene function

Gene product	Virion location	Function
Nucleoprotein (N or NP)	Nucleocapsid	Protects RNA genome
Polymerase phosphoprotein (P)	Associated with nucleocapsid	RNA polymerase subunit
Matrix (M)	Between nucleocapsid and envelope	Virion assembly
Fusion factor (F)	Transmembrane envelope glycoprotein	Fusion and entry
Hemagglutinin-neuraminidase (HN); hemagglutinin (H); glycoprotein (G)	Transmembrane envelope glycoprotein	Viral attachment protein
Large protein (L)	Associated with nucleocapsid	RNA polymerase

Mononegavirales replication



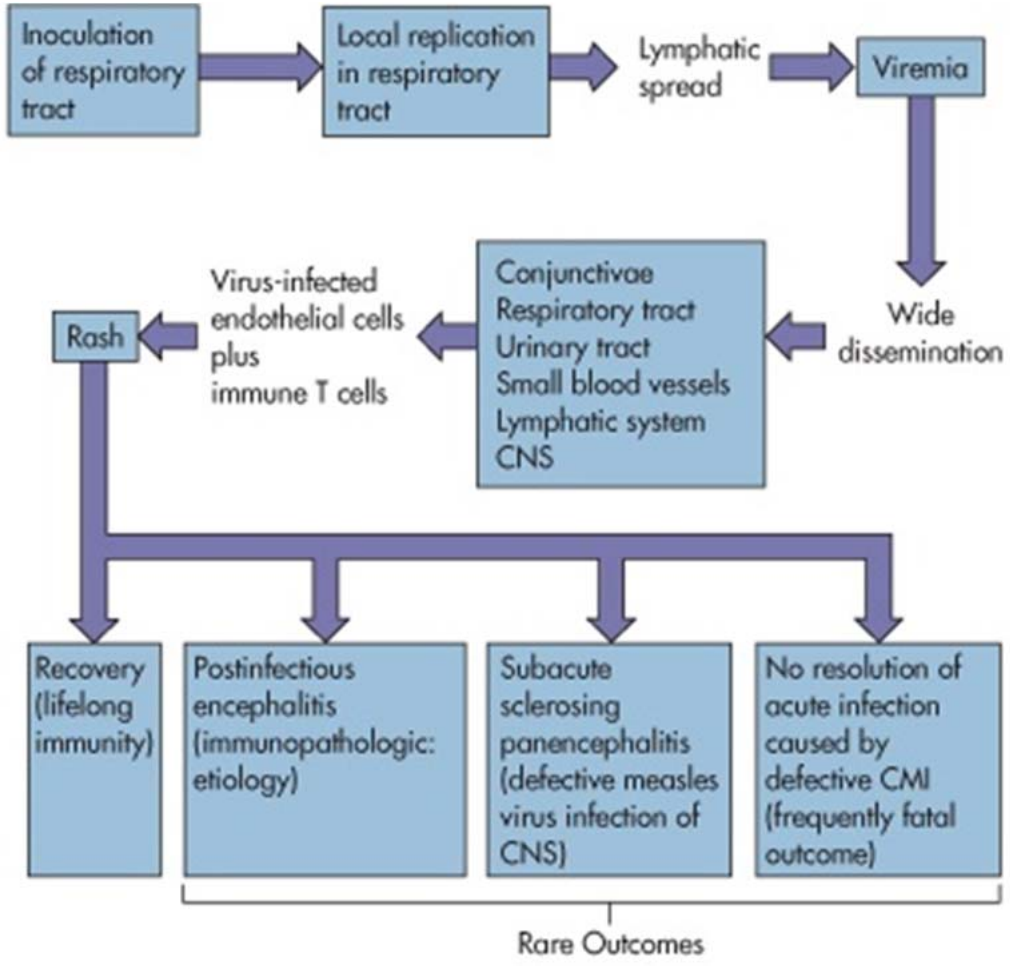
From Schaechter's Mechanisms of Microbial Disease; 4th ed.; Engleberg, DiRita & Dermody; Lippincott, Williams & Wilkins; 2007; Fig. 34-2

- Entirely cytoplasmic
- Attachment by HN/H/G protein to cells - neutralizing antibody is directed against HN/H/G
- Fusion of viral envelope with cell membrane via F protein results in entry
  - Fusion results in giant cell formation (syncytia)
  - Antibody to F to prevents spread of virus from cell to cell
- Virion RNA polymerase directed viral mRNA synthesis
- Full length (+) sense anti-genome synthesis and genome replication
- Assembly and budding

Measles: general

- One of the five classical childhood exanthems (eruptive diseases
  - rubella (togavirus)
  - roseola (HHV 6)
  - chickenpox (herpes zoster)
  - fifth disease (parvovirus, B19, erythema infectiosum)
- One of the most prominent causes of disease in unvaccinated populations
  - 30-40 million cases per year
  - 1-2 million deaths per year
- Fewer than 1000 cases in US since 1993; result of live vaccine
- Host range limited to humans, one serotype

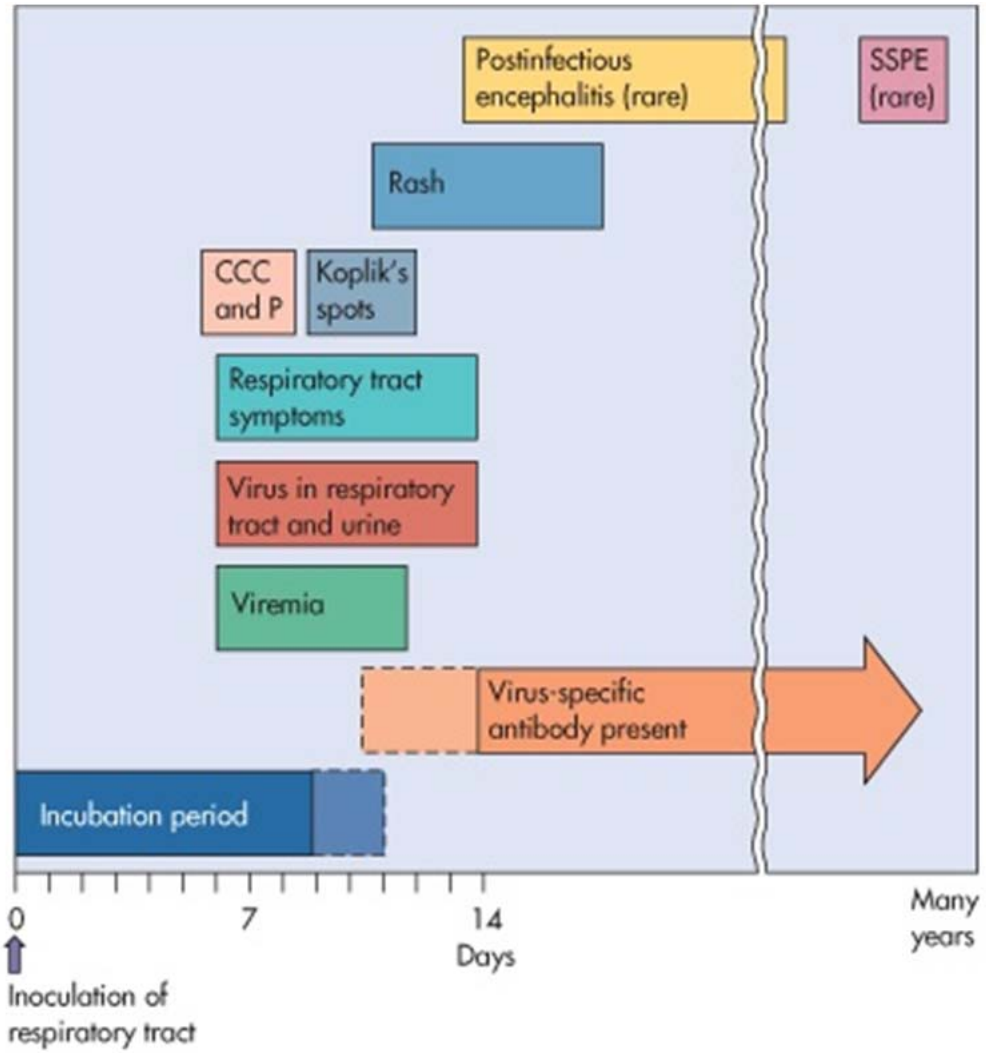
Measles pathogenesis



Mechanisms of spread of the measles virus within the body and the pathogenesis of measles. CMI, Cell-mediated immunity; CNS, central nervous system. (From Medical Microbiology, 5th ed., Murray, Rosenthal & Pfaller, Mosby Inc., 2005, Fig. 59-3.)

- Extremely contagious
- Rarely an inapparent infection
- More severe in adults than children
- Recovery in most cases
- Lifelong immunity
- Complications
  - Viral or bacterial pneumonia
  - Atypical measles
    - Immune sensitization due to an early inactivated viral vaccine (1963-67) or (rarely) attenuated vaccine
    - enhanced immunopathology
  - Acute post-infectious encephalitis (or ADEM- acute disseminated encephalomyelitis)
    - 5-7 days after rash
    - demyelinating autoimmune disease
  - SSPE - subacute sclerosing panencephalitis
    - years after infection
      - mutant virus
      - lethal persistent brain infection
  - Unresolved infection in immune compromise

Measles time course, symptoms



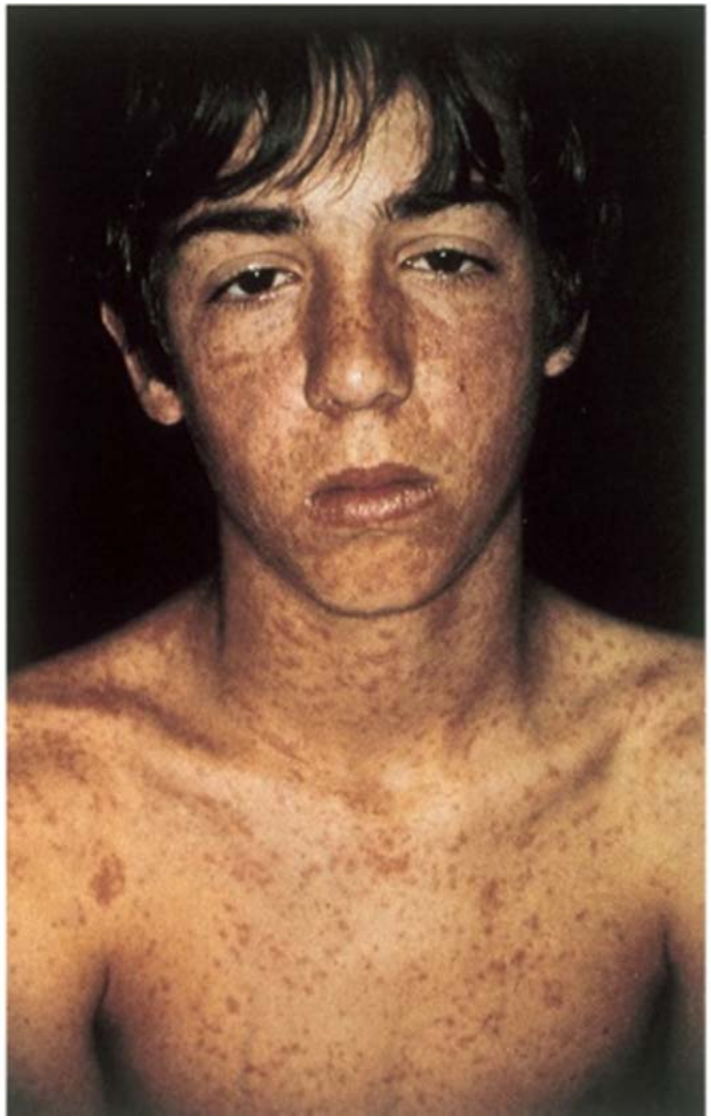
- Contagion during prodrome
- Specific symptoms
  - CCC&P: cough, coryza, conjunctivitis & photophobia
  - Koplik spots - red with white centers on inside of mouth
- Maculopapular rash
  - Duration14 days
  - Spreads from forehead down trunk and out extremities
  - Caused by replication of virus in skin
  - Most symptoms result from immune response to infection
    - T cell deficient patients have no rash

Time course of measles virus infection. Characteristic prodrome symptoms are cough, conjunctivitis, coryza, and photophobia (CCC and P), followed by the appearance of Koplik's spots and rash. SSPE, Subacute sclerosing panencephalitis. (From Medical Microbiology, 5th ed., Murray, Rosenthal & Pfaller, Mosby Inc., 2005, Fig. 59-4.)

Koplik’s spots

Koplik's spots in the mouth and exanthem. Koplik's spots usually precede the measles rash and may be seen for the first day or two after the rash appears. (Courtesy Dr. J.I. Pugh, St. Albans; from Emond RTD, Rowland HAK: *A color atlas of infectious diseases,* ed 3, London, 1995, Mosby.) (From Medical Microbiology, 5th ed., Murray, Rosenthal & Pfaller, Mosby Inc., 2005, Fig. 59-5.)

Measles rash

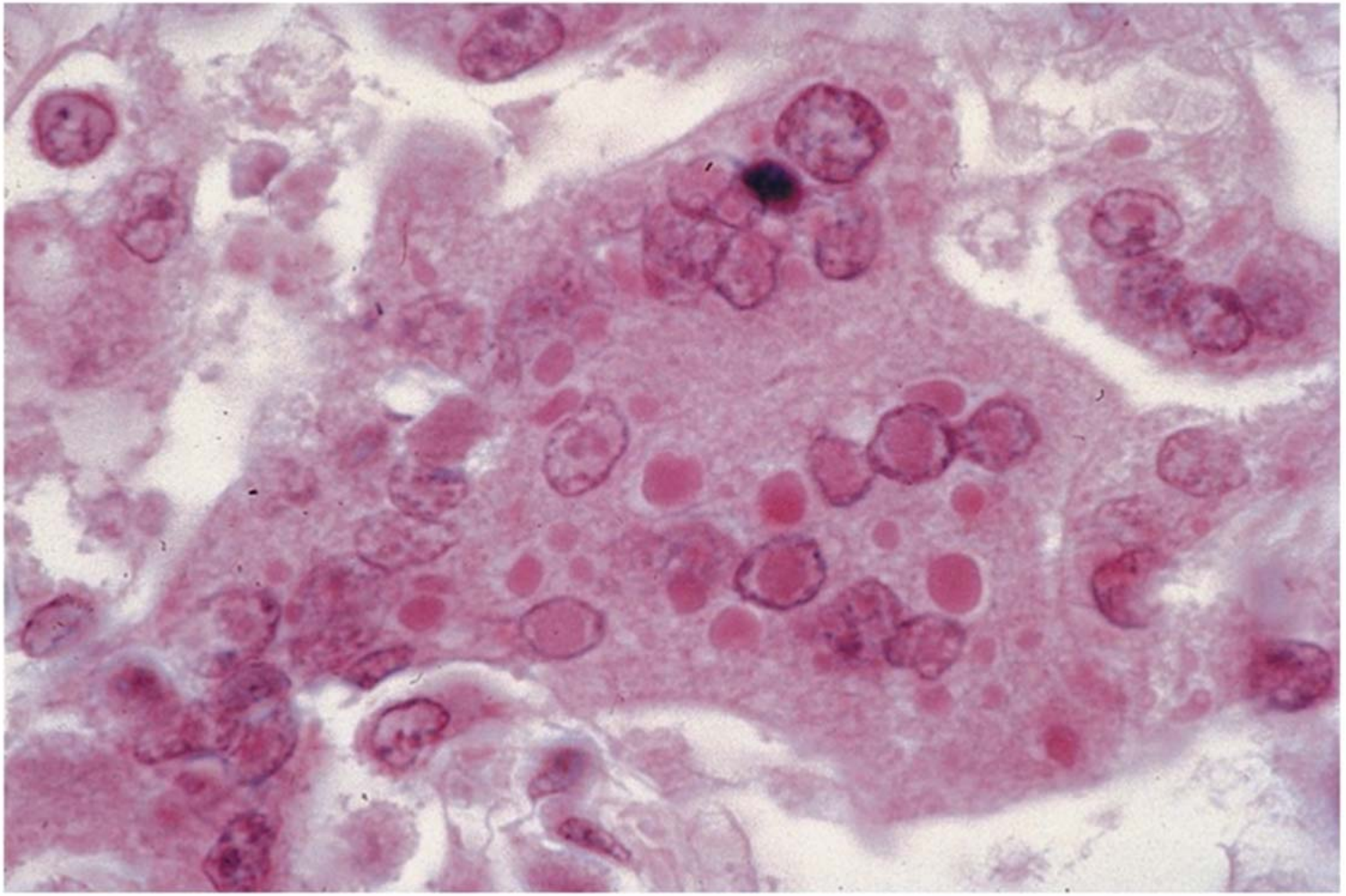


Measles rash. (From Habif TP: *Clinical dermatology: Color guide to diagnosis and therapy,* St Louis, 1985, Mosby.) (From Medical Microbiology, 5th ed., Murray, Rosenthal & Pfaller, Mosby Inc., 2005, Fig. 59-6.)

Measles diagnosis

- Clinical manifestations
  - Koplik's spots
  - Maculopapular rash
  - Fever
  - CCC&P
- Virus culture (difficult)
- Serology for antibody
- rtPCR
- Immunofluorescence for measles antigen

Measles induced syncytia

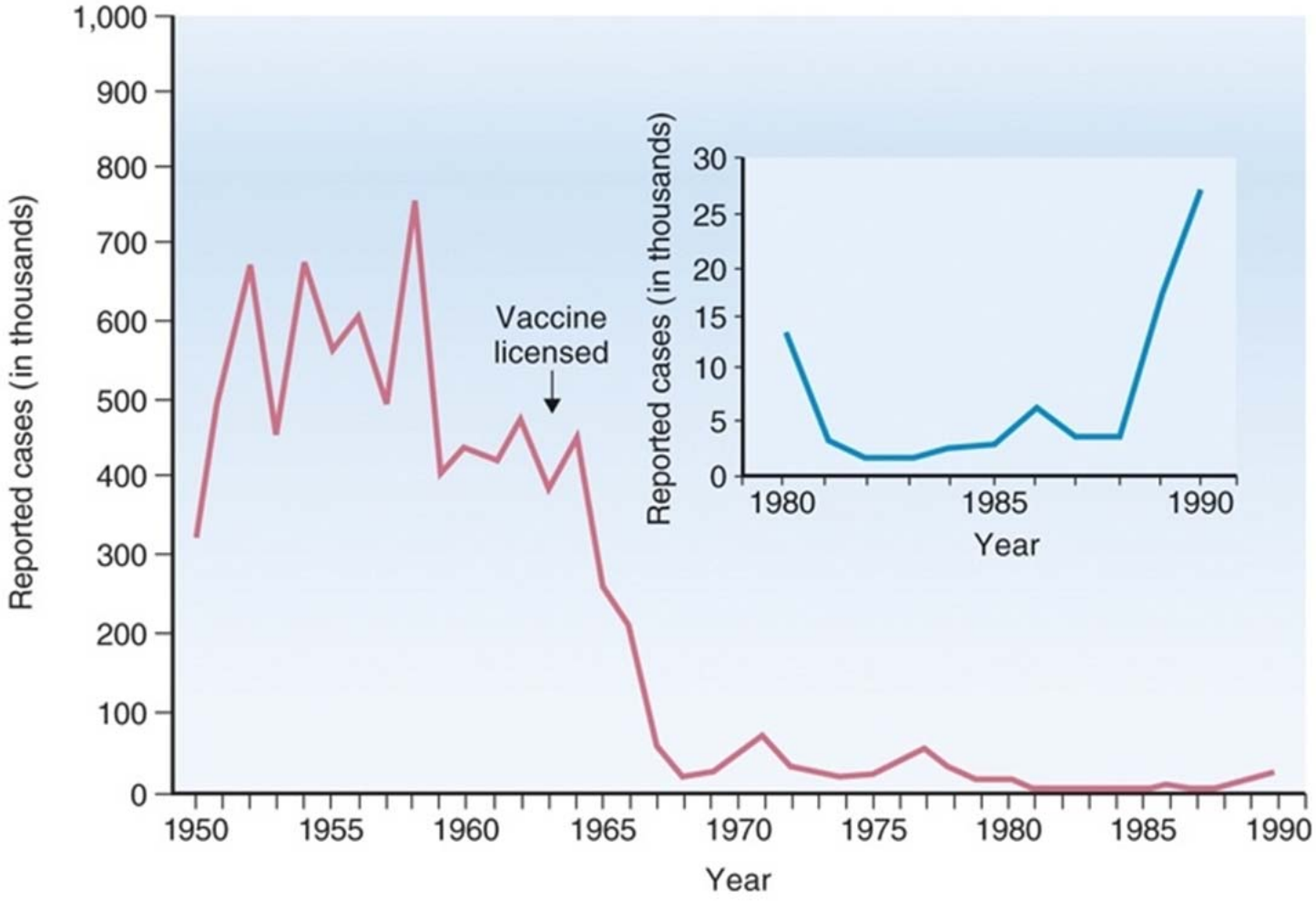


Formation of giant cells (syncytia) in measles pneumonia. Notice the eosinophilic inclusions in both the cytoplasm and nuclei. (From Schaechter's Mechanisms of Microbial Disease; 4th ed.; Engleberg, DiRita & Dermody; Lippincott, Williams & Wilkins; 2007; Fig. 34-3)

Measles vaccination

- Live attenuated vaccine in MMR; injected
- One serotype
- Timing with respect to maternal immunity a consideration
- Antibody response good, but not lifelong as in natural infection
  - Revaccinate at 18-20 yrs. Recent outbreak due to unvaccinated individuals

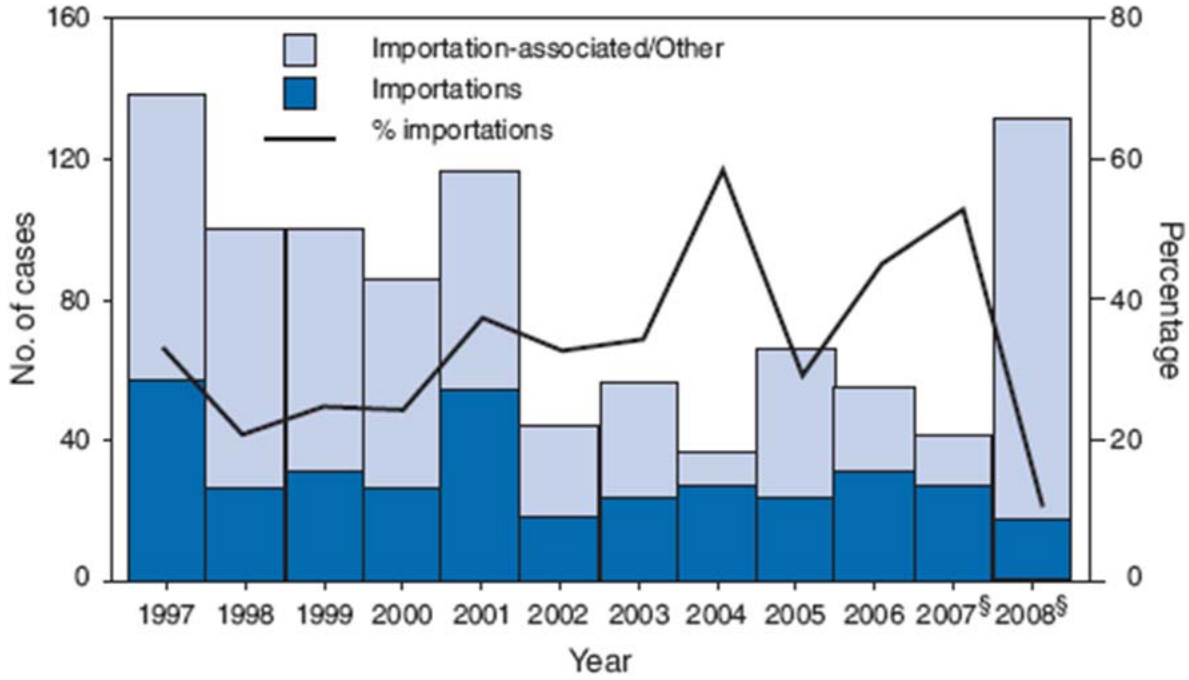
Measles vaccination



Reported cases of measles in the United States, 1950:1990. Immediately after the introduction of the vaccine, the incidence declined dramatically. A measles epidemic occurred between 1989 and 1991, with most cases affecting unvaccinated children younger than 5 years. (From Schaechter's Mechanisms of Microbial Disease; 4th ed.; Engleberg, DiRita & Dermody; Lippincott, Williams & Wilkins; 2007; Fig. 34-6)

Measles: 2008

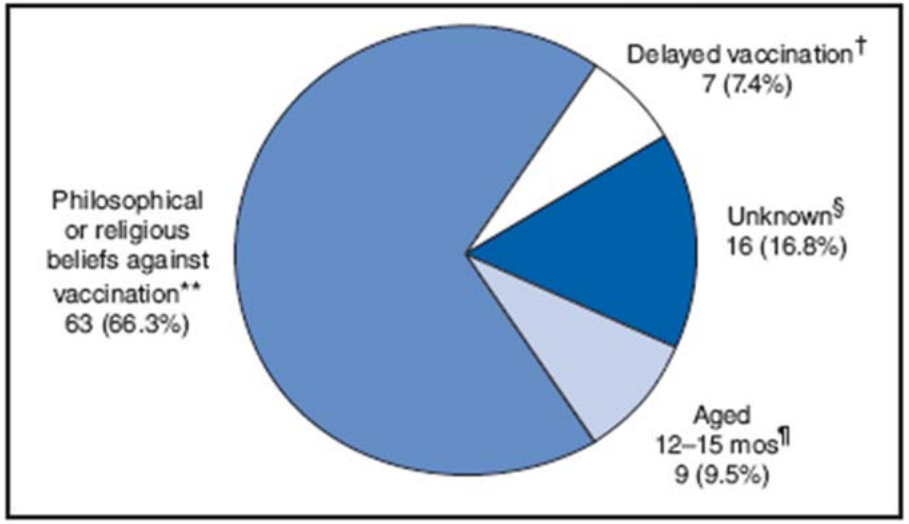
FIGURE 1. Trend in cases of imported measles* as a proportion of all measles cases† — United States, 1997–July 2008



* Measles infection acquired outside of the United States.
† Includes importation, importation-associated (acquired inside the United States but linked epidemiologically to an importation), and other (source unknown) measles cases.
§ Provisional; 2008 data are for January–July only.

Measles: 2008

FIGURE 2. U.S. residents with measles who were eligible* for vaccination against measles, by reason for not receiving measles vaccine — United States, January–July 2008



* N = 95. Does not include infants aged <12 months, persons born before 1957, foreign visitors, and persons who were vaccinated.

† Includes children aged 16 months to 4 years who had not been vaccinated.

§ Includes persons who were age eligible for vaccination but whose vaccination status was unknown or who were unvaccinated for unknown reasons.

¶ Includes eight children eligible for vaccination, but not yet vaccinated, and one child whose vaccination status was unknown.

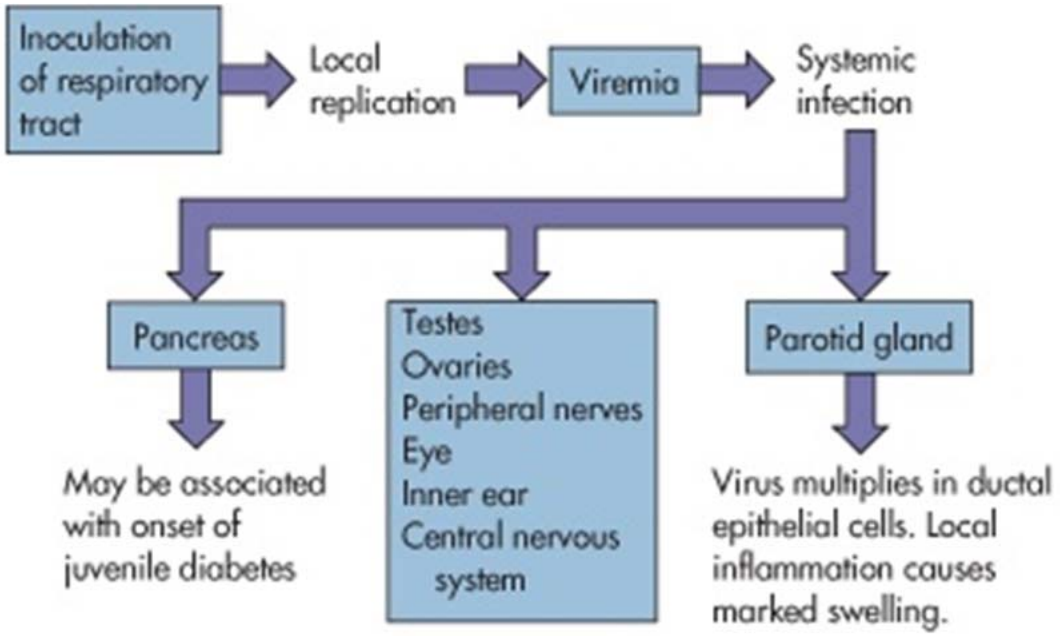
** Includes persons who were unvaccinated because of their own or their parents' beliefs. This category includes 61 persons aged ≤18 years and two persons aged 20–50 years. None of the persons in this category cited medical reasons for not having been vaccinated.

Mumps

Mumps

Child with parotitis. (Centers for Disease Control and Prevention's Public Health Image Library (PHIL); CDC/NIP/Barbara Rice

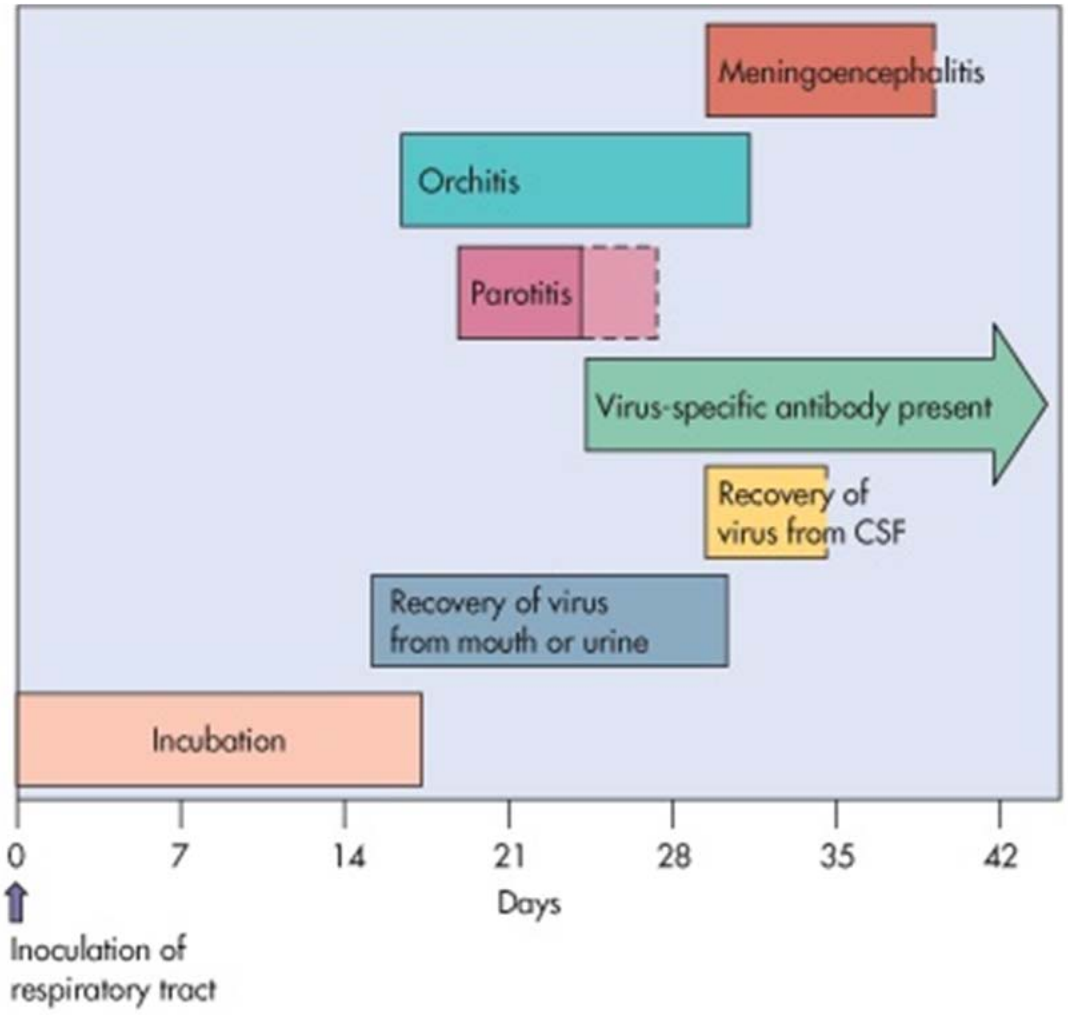
Mumps pathogenesis



Mechanism of spread of mumps virus within the body. (From Medical Microbiology, 5th ed., Murray, Rosenthal & Pfaller, Mosby Inc., 2005, Fig. 59-7.)

- Respiratory transmission
  - Less contagious than measles
- Prodrome: sore throat, cough
  - Contagion period precedes symptoms.
- Spread
  - Replication in lymph nodes
  - Viremia
  - Primary target organ is parotid (salivary) gland at 18-21 days
- Symptoms
  - Parotid gland swelling due to edema and local inflammatory response
  - 10% not bilateral, some have no swelling at all.
  - Also causes swelling in testes, ovaries. Can cause sterility in males
  - 30% inapparent infections
- CNS complications: aseptic meningitis, but full recovery, rarely encephalitis

Mumps time course



Time course of mumps virus infection. (From Medical Microbiology, 5th ed., Murray, Rosenthal & Pfaller, Mosby Inc., 2005, Fig. 59-8.)

Mumps diagnosis

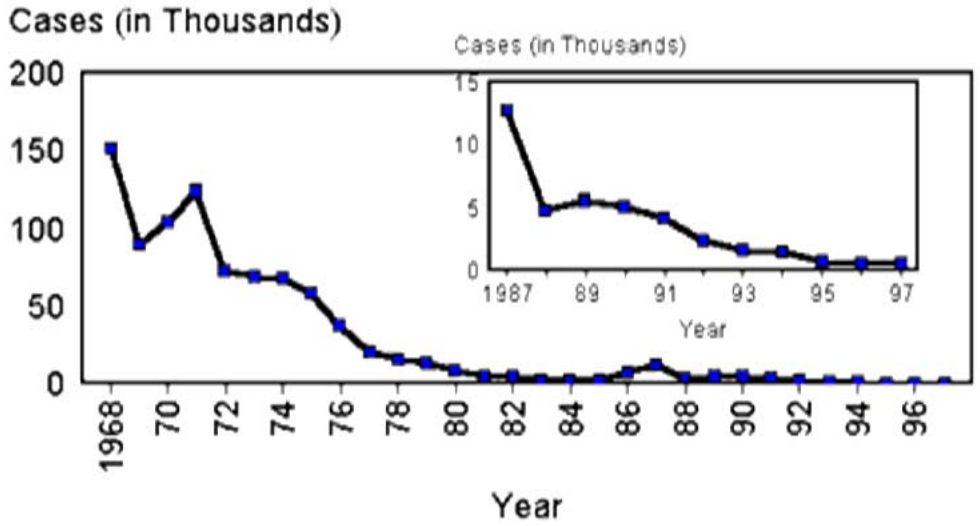
- Clinical
- Serology
- Culture
- Hemadsorption

Mumps vaccination

Reported mumps cases, United States, 1968-1997

Mumps vaccine reduced mumps cases by 99.57%

http://www.hhs.gov/nvpo/concepts/intro6.htm



- Live attenuated vaccine in MMR; injected
- One serotype
- 80% effective with one dose, 90% effective with two doses

Recent mumps outbreaks

- 2006: 6584 cases in Midwestern US mostly in vaccinated college students in dormitories
- 2006-2009: return to normal levels (100-200/yr)
- 2009: 1521 cases in New York & New Jersey in a summer camp for tradition-observant Jewish boys, mostly vaccinated
- Occurred in congregate settings, where prolonged, close contact among persons might be facilitating transmission
- In cases, index cases were imported from UK where vaccination rates have recently been low resulting in epidemic mumps

Vaccines and autism

- 1998: a British gastroenterologist, Andrew Wakefield, M.D. authors Lancet article suggesting that the measles, mumps, and rubella (MMR) vaccine might cause symptoms associated with autism
  - Case study of eight children who had received the MMR and then developed symptoms of autism
- Eighteen subsequent controlled epidemiological studies find no link between MMR or thimerosal (preservative) and autism
- 2004: Institute of Medicine concluded: "the body of epidemiological evidence favors rejection of a causal relationship" between both the MMR vaccine and thimerosal, and autism
- 2004: 10 of the 13 authors of the Wakefield study retracted it
- February 2010: The Lancet retracted Wakefield's entire study after an independent government review concluded that he had acted "dishonestly and irresponsibly" in conducting his research
- May 2010, Wakefield banned from practicing medicine in the UK

Respiratory syncytial virus disease & immunity

- Widespread: 75% of infants seropositive by 1 year of age
- Yearly in US 50,000-80,000 hospitalizations, 100 infant deaths, 17,000 elderly deaths
  - Most common cause of fatal acute respiratory tract infections in infants and young children
- Host range limited to humans; single serotype
- Respiratory transmission
  - Aerosol droplets or fomites, hand to nose contact, usually in the winter months
  - Highly contagious; contagion period precedes symptoms and may occur in absence of symptoms
- Localized infections of respiratory tract, no viremia and no systemic infections
- Disease
  - Children < 1 y.o.: bronchiolitis
    - Wheezing, dyspnea, air trapping, hyperexpansion of lung, decreased ventilation; resembles asthma
    - Caused by host immune response, particularly severe in infants, resembles asthma and blocks airways. Unusual in that severe infection occurs in first year in the face of maternal antibody. Also causes pneumonia
  - Pneumonia
  - Common cold in older children and adults
- Poor immunity
  - Reinfection occurs throughout life
  - Maternal antibody does not prevent infection

Respiratory syncytial virus diagnosis & treatment

- Diagnosis
  - rtPCR, immunofluorescence, enzyme immunoassay, serology
  - Culture difficult
- Treatment
  - Ribavarin reduces severity of symptoms in immunocompromised patients
- No vaccine; improper vaccination increases severity of disease
- Passive vaccination for high risk infants
  - Palivizumab: anti-F monoclonal antibody

Parainfluenza viruses

- Four serotypes, host range limited to humans,
- Respiratory transmission
- Infections limited to respiratory tract, generally non-systemic and viremia rare
- Causes cold-like symptoms, bronchitis and croup (serotypes 1 and 2). Infections of children common
- Diagnosis
  - Virus culture
  - Syncytia formation
  - Hemadsorption
  - Hemagglutination inhibition
  - rtPCR
- Immunity following infection short-lived. Individuals subject to re-infection
- Candidate vaccines are in various stages of clinical trials

Human metapneumovirus

- Newly discovered
- Respiratory transmission
- Disease: asymptomatic, common cold, bronchiolitis, pneumonia
  - Accounts for 15% of common colds in children
- Diagnosis by rtPCR

Paramyxovirus summary

- Structure
  - Negative sense ssRNA genome, helical nucleocapsid, envelope with attachment protein and F protein
- Pathogenesis
  - Transmission in respiratory droplets and fusion of virus envelope via F protein with plasma membrane of cells in the respiratory tract
  - Replication in cytoplasm, budding
  - Viremia except for RSV and PIV
  - Innate and antibody response important; many symptoms from immune response: rash in measles and swelling in mumps; PIV bronchitis and croup; RSV bronchiolitis and pneumonia in infants
  - Sequelae in CNS for measles and mumps
- Diagnosis
  - Serology or nucleic acid
  - Measles: Koplik spots; mumps: swelling of parotid gland
- Treatment/prevention
  - MMR live attenuated viral vaccine for measles and mumps, none for RSV or PIV