

## Virus Pathogenesis & Virus Genetics

Reading: Schaechter's Mechanisms of Microbial Disease, 4<sup>th</sup> edition, 2007, Engleberg, DiRita & Dermody. Chapter 31.

### I. Definitions

#### A. Tropism

1. what cells within the host does the virus infect?
2. influenced by cellular receptors, intracellular molecular restrictions, route of infection & spread

#### B. Prodrome

1. early disease symptoms which are mild or non-specific

#### C. Fomite

1. an inanimate object or substance that is capable of transmitting infectious organisms from one individual to another

### II. Cycle of infection

#### A. Entry

1. Virus enters through mucous membranes or skin
2. Respiratory, oral, sexual, percutaneous (needles, wounds, bites)

#### B. Primary site replication

#### C. Spread

1. Local, blood (viremia), neural, lymphatic

#### D. Secondary site replication; target tissue

#### E. Shedding, transmission

1. Routes: respiratory, gastrointestinal (oral-fecal), urogenital, skin
2. Mechanisms
  - a. Indirect contact: aerosols, fomites
  - b. Direct contact; lesions, saliva, sex, animal or insect bites, maternal-neonatal

### III. Effects on cells

#### A. Abortive, lytic, persistent, transforming infections

#### B. Alteration of cellular metabolism

### IV. Effects on organism

#### A. Duration, prodrome varies depending on whether or not the infection spreads

#### B. Immune response; immunopathology

1. Innate vs. adaptive response
2. Hypersensitivity and inflammation are major causes of disease symptoms
3. Virus response

#### C. Types of infection: asymptomatic, acute, latent, chronic

### V. Genetics

#### A. Standard genetic concepts apply to viruses: mutation, recombination, genotype, phenotype, selection

#### B. Scope of virus genetics

1. Natural evolution of viruses
2. Clinical management of virus infections
3. Experimental virology

- C. Genetics important in a clinical setting
  - 1. Variation in HIV and flu impacts on vaccination
  - 2. Drug resistance in herpes and HIV
  - 3. Reversion of attenuation in polio
  - 4. Genetic manipulation useful for creating new vaccines: temperature sensitive influenza (Flumist)
- D. Mutation
  - 1. DNA viruses mutate less than RNA viruses
    - a. RNA virus polymerases have no proofreading function
    - b. RNA virus "quasi species" are adaptable
- E. Mutant phenotypes
  - 1. Temperature sensitive
    - a. Usually growth at low but not high temperature
  - 2. Drug resistance
- F. Spontaneous mutation, reversion
- G. Recombination, reassortment
  - 1. DNA viruses
    - a. Breaking and joining
  - 2. Non-segmented RNA viruses
    - a. "copy choice"
  - 3. Segmented RNA viruses
    - a. "reassortment"
  - 4. Impact
    - a. Intrinsically interesting
    - b. Virus evolution
    - c. Laboratory virology
- VI. Viral vaccines
  - A. Live, attenuated
    - 1. Naturally or artificially reduced in pathogenicity in humans
  - B. Killed, inactivated
    - 1. Wild type virus, chemically inactivated
  - C. Subunit
    - 1. Part of the virus, either natural or synthetic
- VII. Antiviral drugs
  - A. Must target virus specific functions and not kill the host.

# Virus pathogenesis and genetics

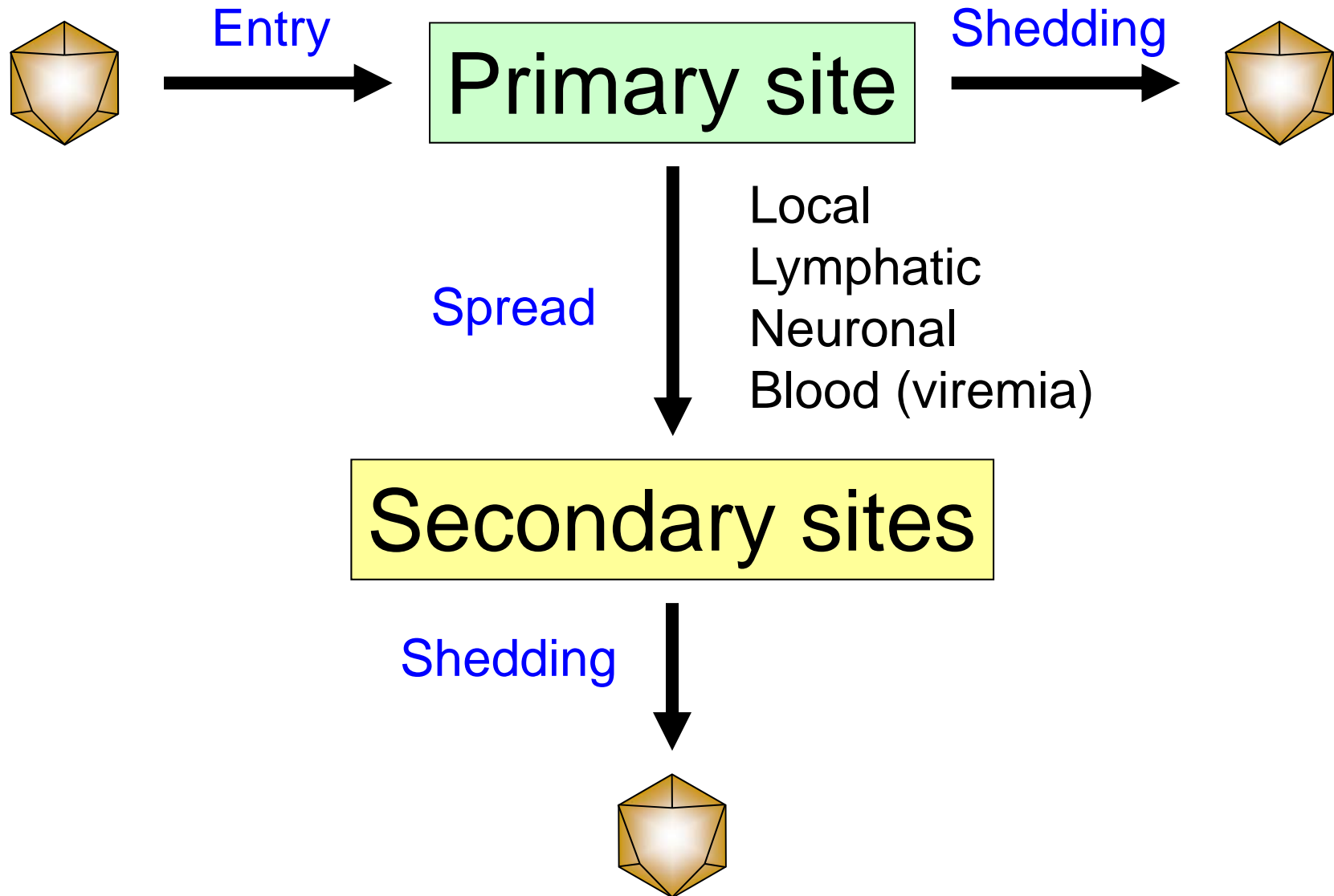
# Viral pathogenesis

- Cycle of infection
  - Entry
  - Primary site replication
  - Spread within the host
  - Shedding
  - Transmission
- Effects on cells
- Effects on organism

# Definitions

- Tropism
  - what cells within the host does the virus infect?
  - influenced by cellular receptors, intracellular molecular restrictions, route of infection & spread
- Prodrome
  - early disease symptoms which are mild or non-specific
- Fomite
  - an inanimate object or substance that is capable of transmitting infectious organisms from one individual to another

# Cycle of infection



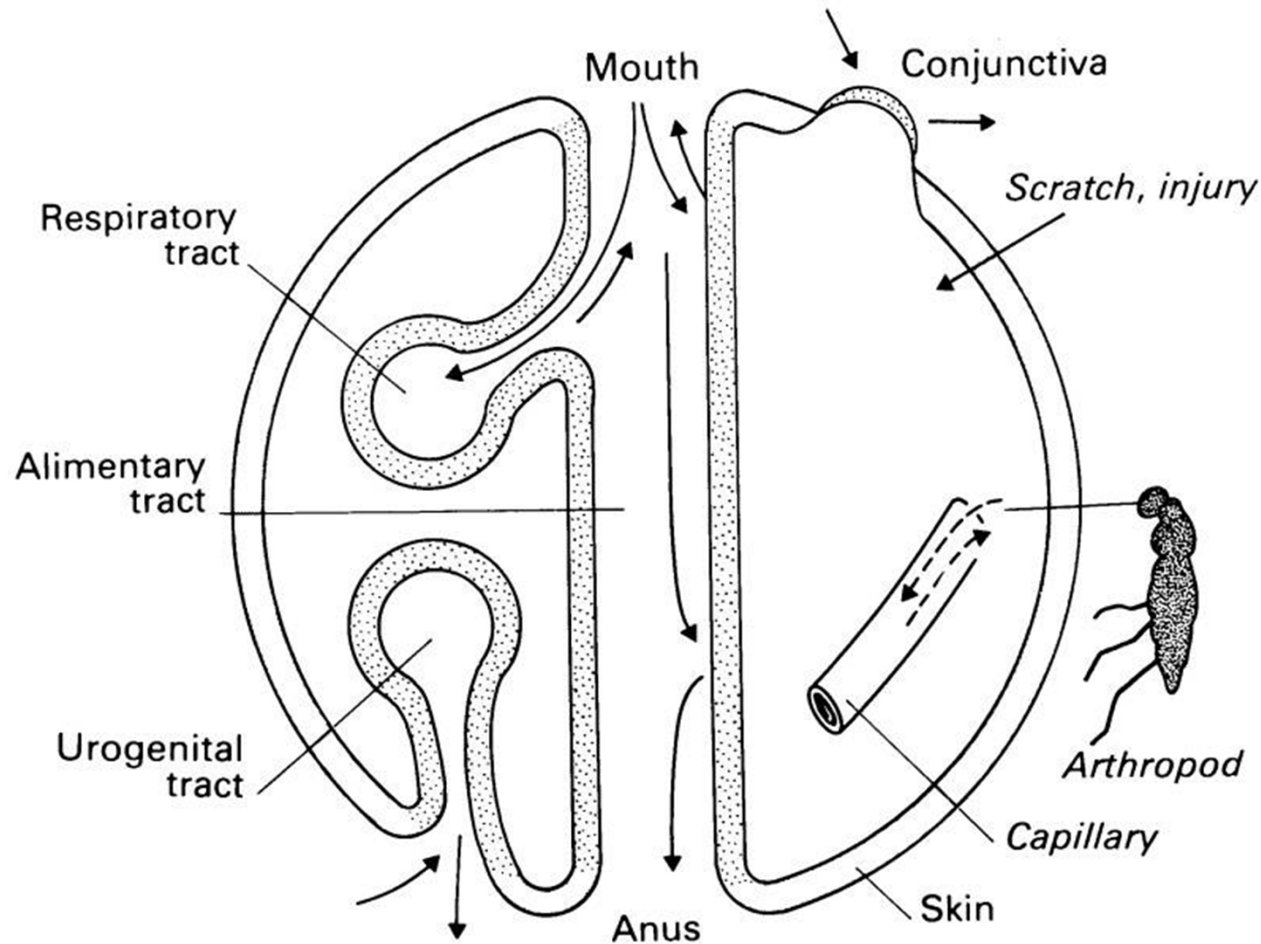
# Entry

- Mucous membranes or skin
  - Respiratory
  - Oral
  - Sexual
  - Ocular
  - Percutaneous
    - needles, wounds, bites

# Shedding, transmission

- Routes
  - Respiratory
  - Gastrointestinal (oral-fecal)
  - Urogenital
  - Skin
- Mechanisms
  - Indirect contact
    - Aerosols
    - Fomites
  - Direct contact
    - Lesions
    - Saliva
    - Sex
    - Animal or insect bites
    - Maternal-neonatal

# Routes of entry and shedding



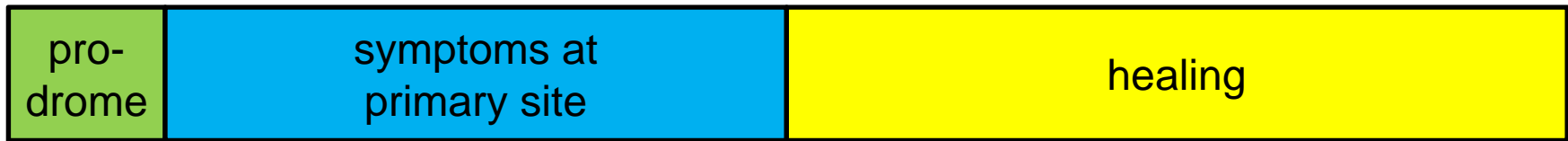
Portals of entry of viruses into the host, and sites of shedding from the host. (From Fields Virology, 4th ed, Knipe & Howley, eds, Lippincott Williams & Wilkins, 2001, Figure 9-2)

# Effects on cells

- Abortive infection
- Lytic infection
- Persistence
- Transformation
- Alteration of cellular metabolism

# Time course of infection; host response

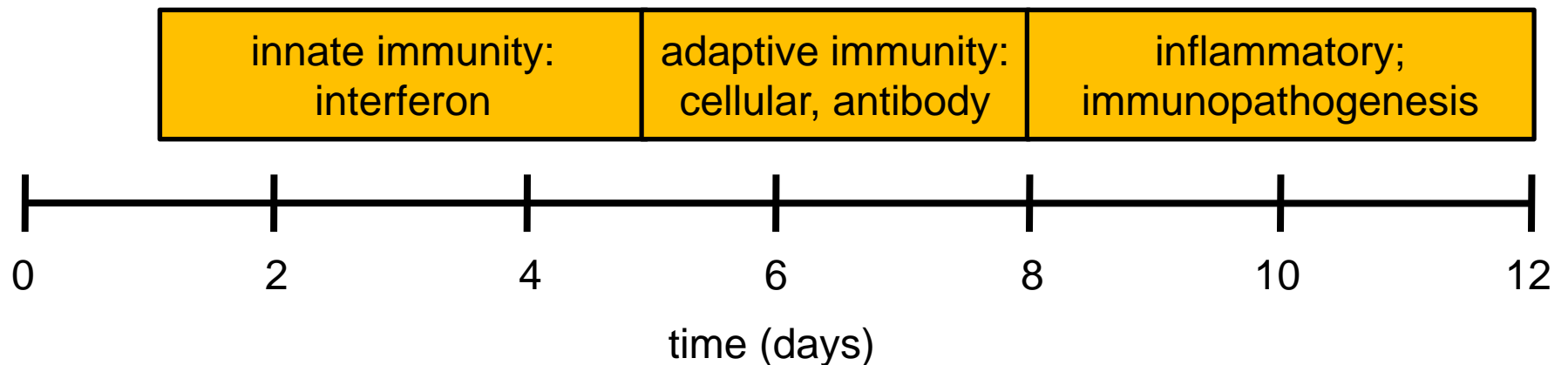
infection without spread:



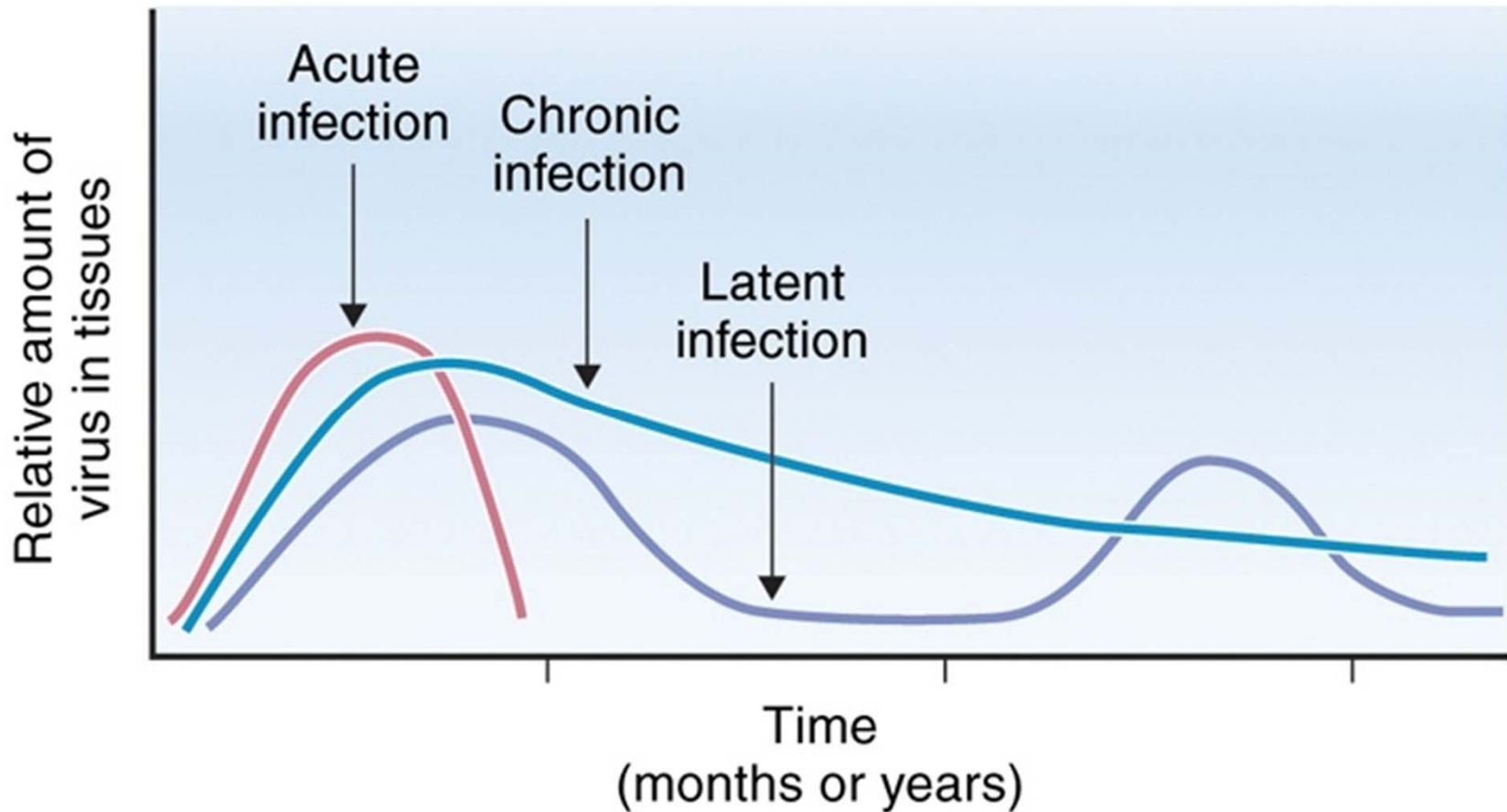
infection with spread:



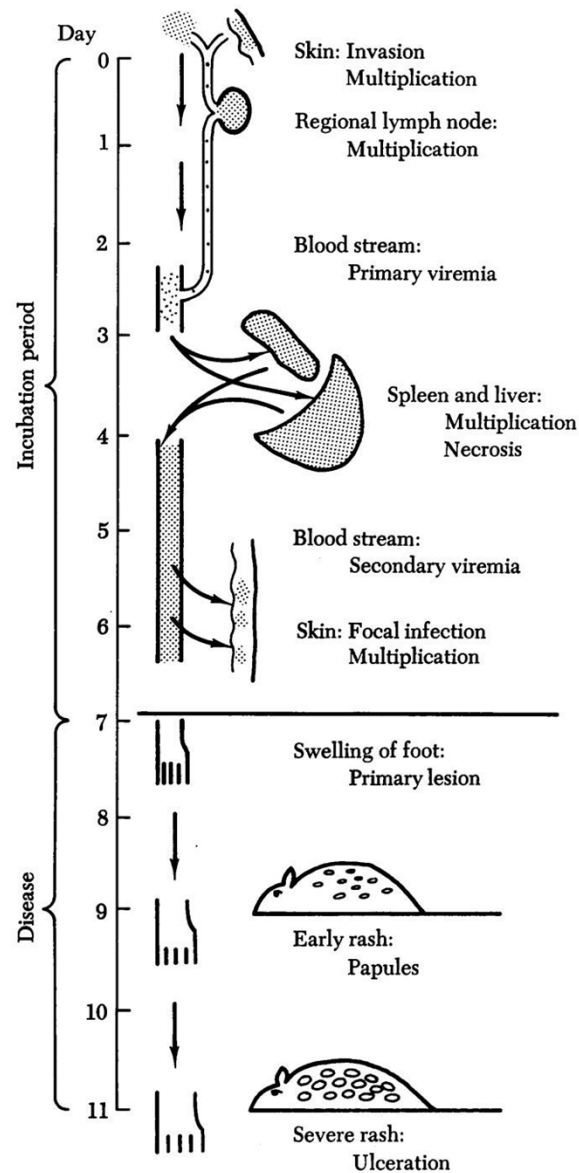
host response:



# Patterns of disease



# Mousepox pathogenesis



The pathogenesis of mousepox (ectromelia). (From Fields Virology, 4th ed, Knipe & Howley, eds, Lippincott Williams & Wilkins, 2001, Figure 9-6)

# Genetic principles

- Mutation
- Recombination
- Genotype
- Phenotype
- Selection

# Scope of virus genetics

- Natural evolution of viruses
- Clinical management of virus infections
- Experimental virology

# Clinical significance of genetics

- Antigenic variation in HIV and influenza
  - impact on vaccination
- Drug resistance in herpes and HIV
- Reversion of attenuation in polio vaccine
- Engineered vaccines
  - temperature sensitive influenza (Flumist)

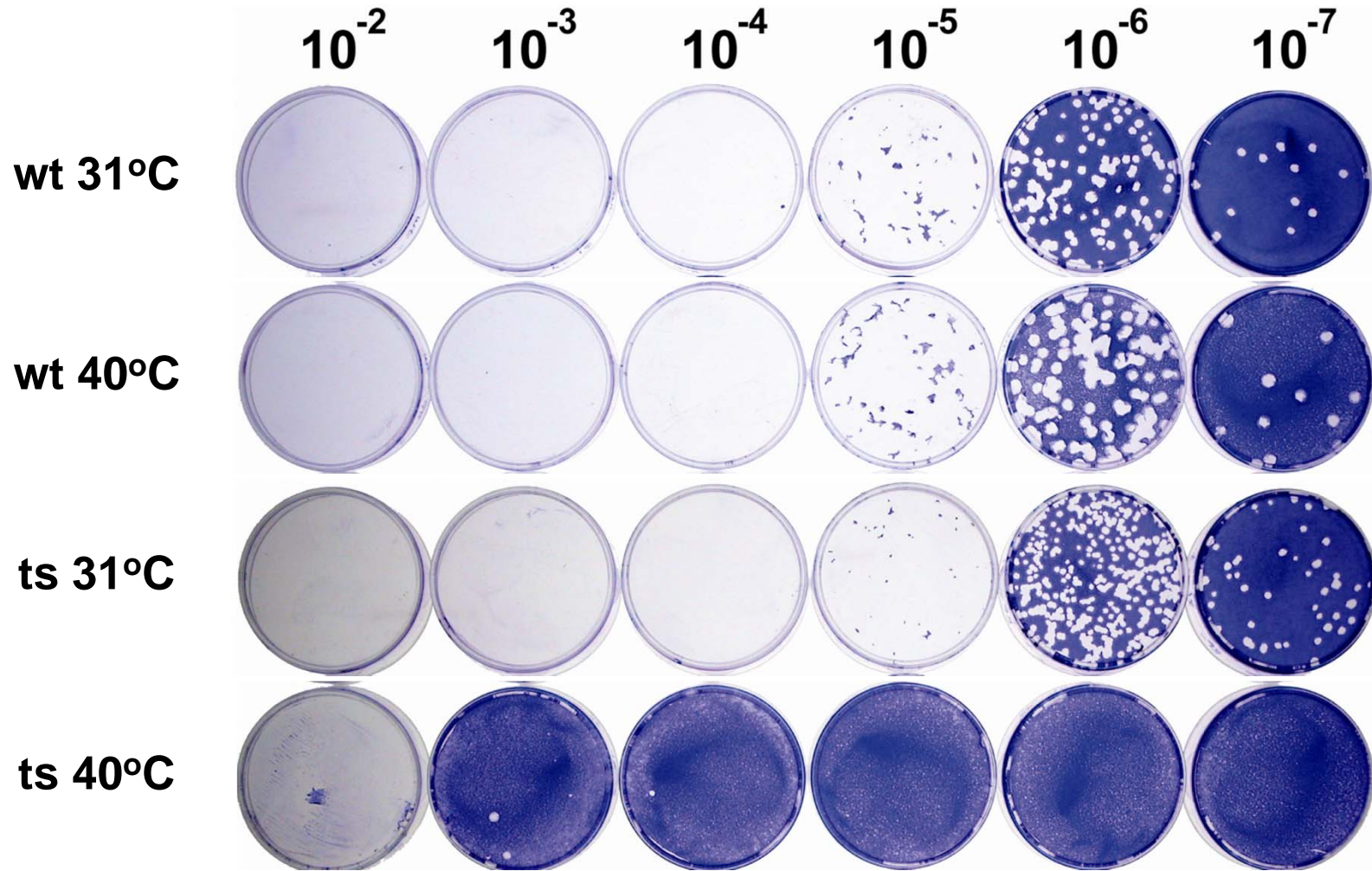
# Mutation

- RNA virus polymerases lack proofreading function
- RNA viruses mutate more frequently than DNA viruses
- RNA virus "quasi species" are adaptable

# Mutant phenotypes

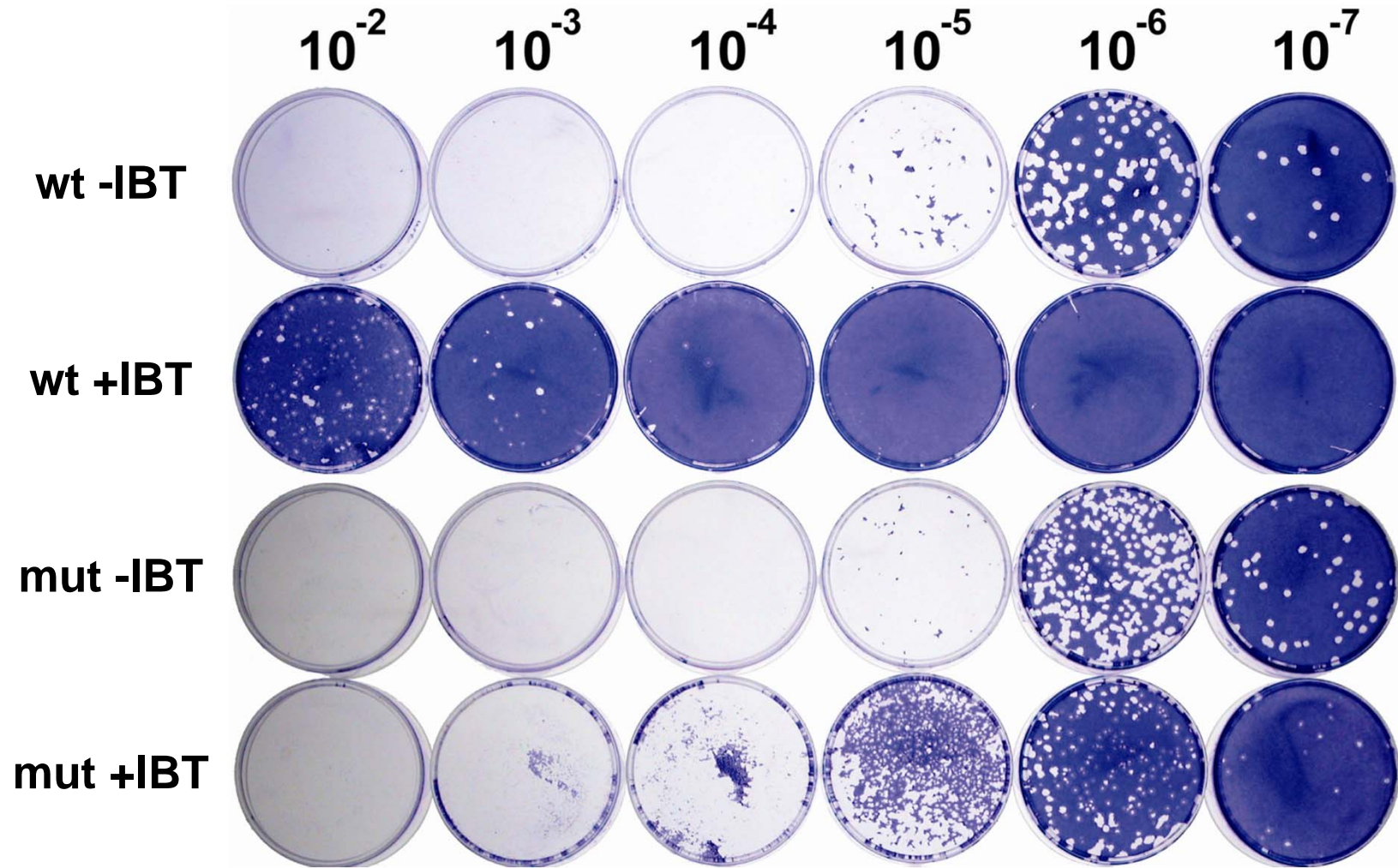
- Temperature sensitive
  - Usually growth at low but not high temperature
- Drug resistance

# Temperature sensitivity



Note spontaneous reversion

# Drug resistance

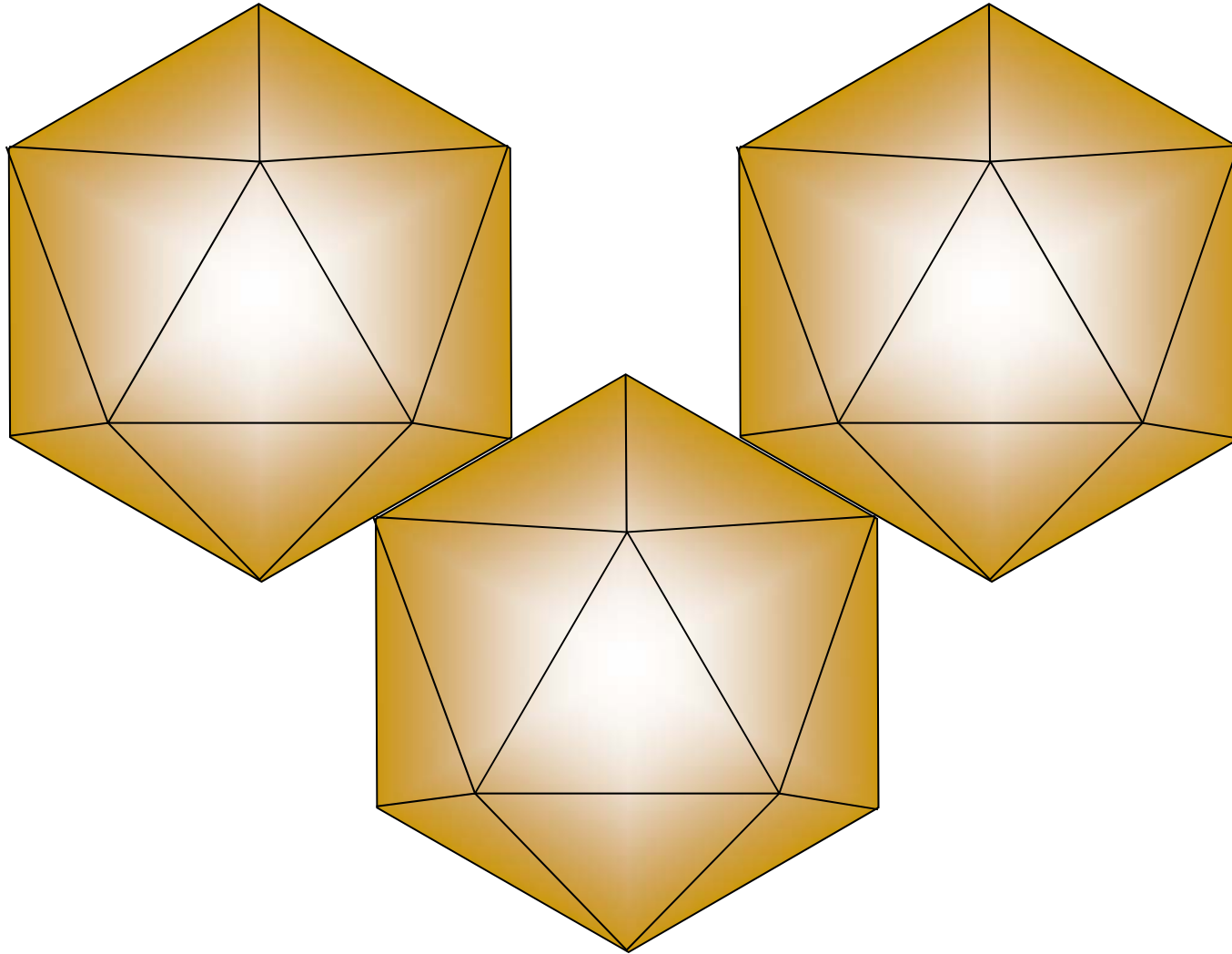


Note spontaneous resistance

# Recombination and reassortment

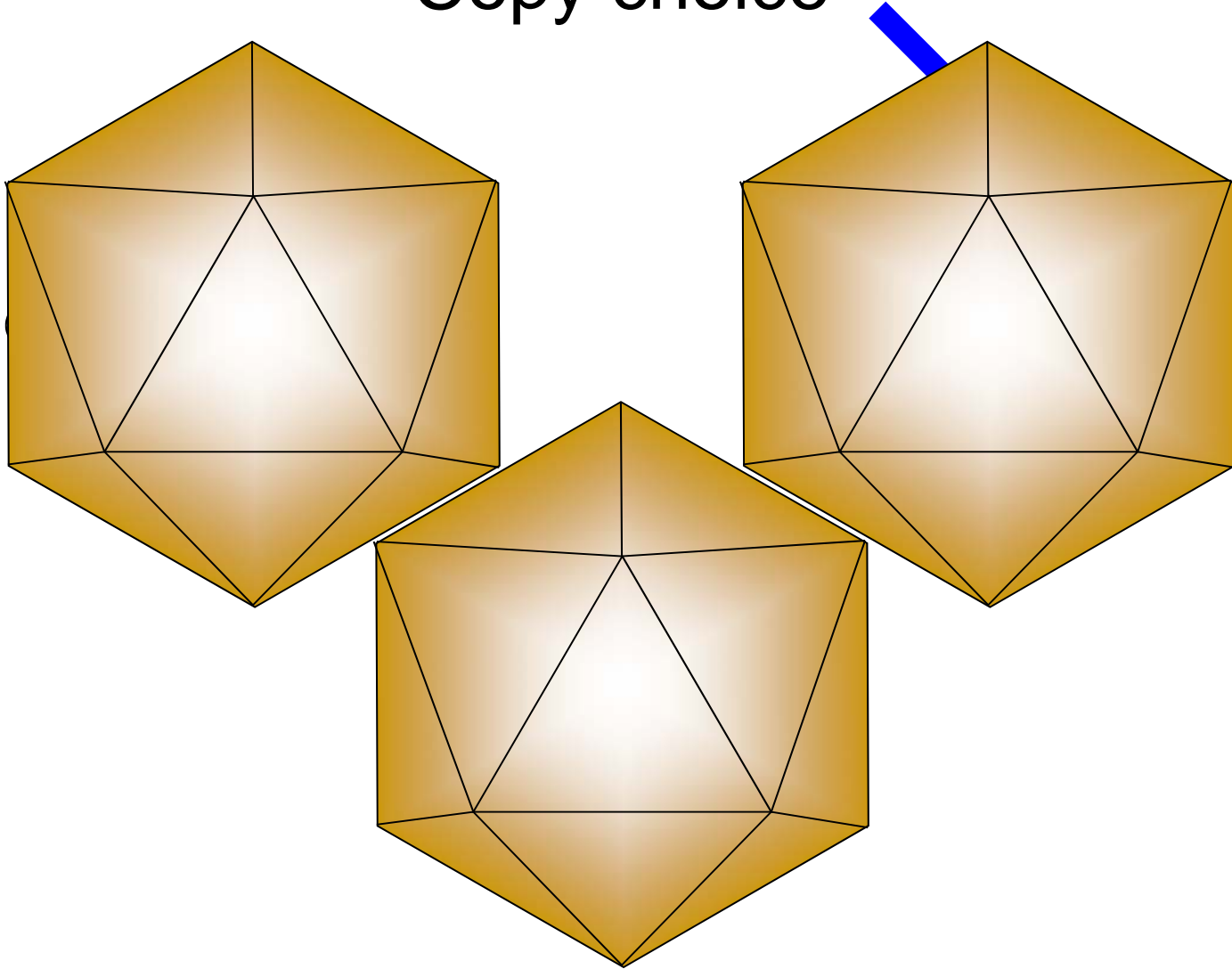
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  - Breaking and joining
- Non-segmented RNA viruses
  - “copy choice”
- Segmented RNA viruses
  - “reassortment”
- Impact
  - Intrinsically interesting
  - Virus evolution
  - Laboratory virology

# DNA virus recombination

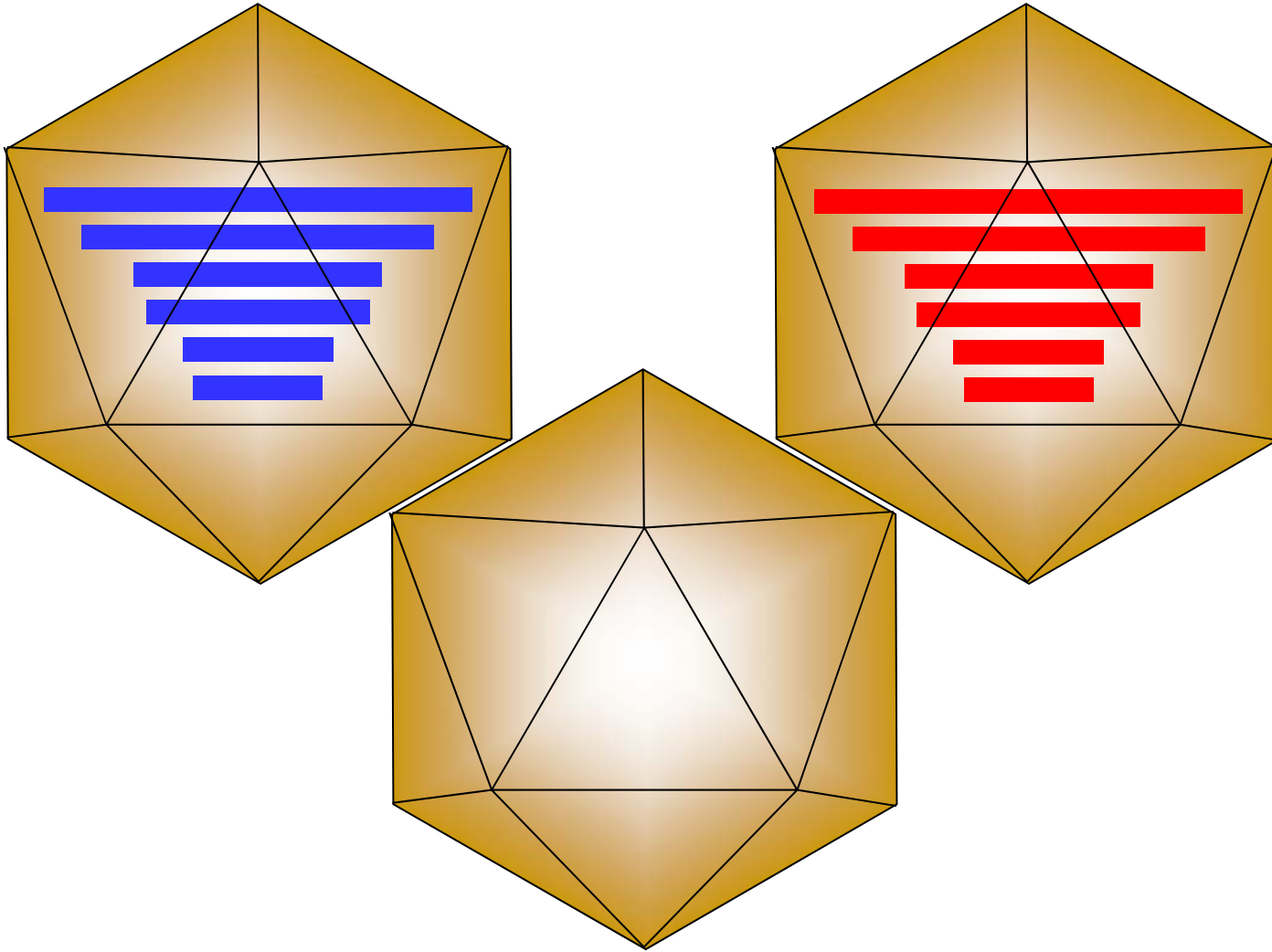


# RNA virus recombination

Copy choice



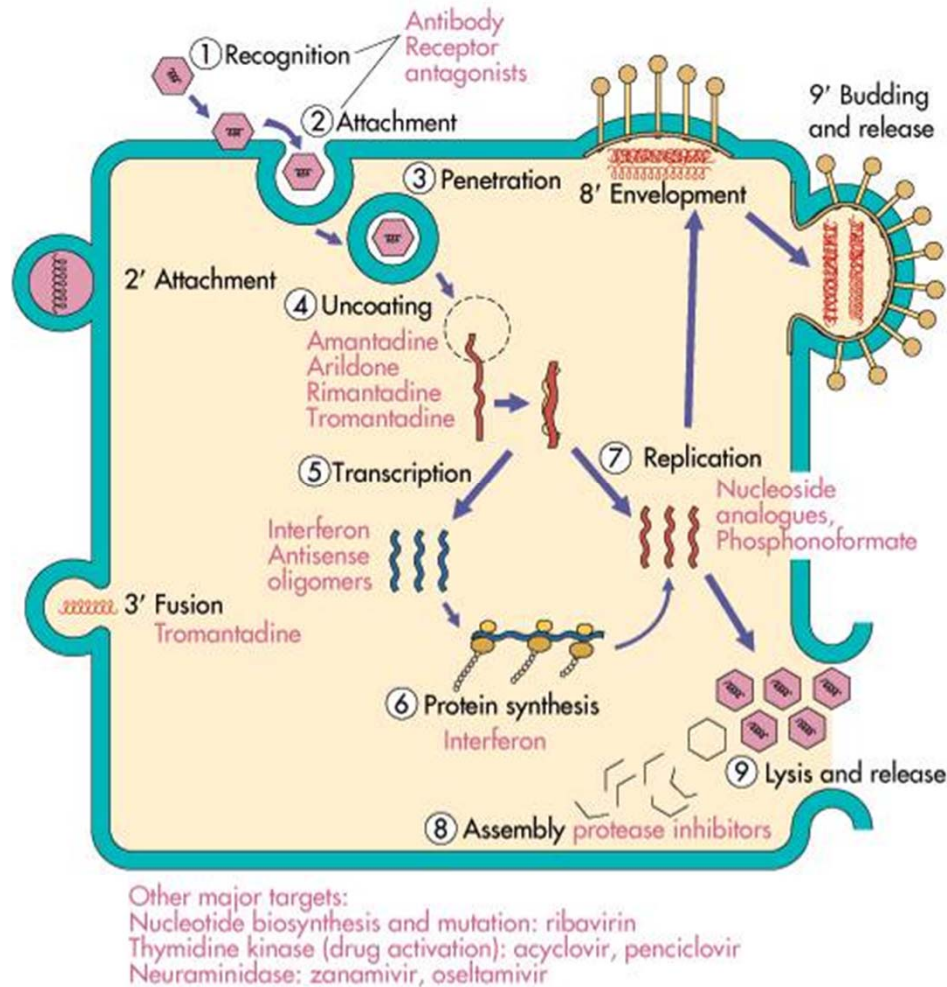
# RNA virus reassortment



# Viral vaccines

- Live, attenuated
  - Naturally or artificially reduced in pathogenicity for humans
- Killed, inactivated
  - Wild type virus, chemically inactivated
- Subunit
  - Part of the virus, either natural or synthetic

# Antiviral drugs



Must target virus specific functions and not kill the host

A general scheme of viral replication. Enveloped viruses have alternative means of entry (3) assembly, and exit from the cell (8' and 9'). The antiviral drugs for susceptible steps in viral replication susceptible to antiviral drugs are listed in magenta. (From Medical Microbiology, 5th ed., Murray, Rosenthal & Pfaller, Mosby Inc., 2005, Fig. 6-9)

# Summary:

## Pathogenesis & Genetics

- Cycle of infection
- Effects on cells
  - Abortive, lytic, persistent, latent, transforming infections
- Effects on the organism
- Genetics
  - Mutation, genotype, phenotype, reversion, recombination
- Vaccines
- Antiviral drugs

*Don't go yet.....*

# For each virus, know:

- Structure
- Pathogenesis
  - transmission/entry/shedding
  - replication
  - spread
  - immune response/counter response
  - damage/disease mechanism
- Diagnosis
- Treatment/prevention
  - drugs
  - vaccines