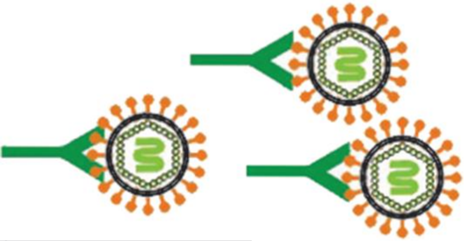
11

Vaccines



Antiviral Vaccines

- Definition:
  - **Antiviral vaccine**: Any preparation used as a preventive inoculation to confer immunity against a specific virus
  - **Vaccination**: Administration of a vaccine to a person (usually by injection)
  - **Immunization**: The event that happens in one’s body after vaccination. The vaccine stimulates one’s immune system so that it can recognize the disease and offer protection from future infection

A brief history of antiviral vaccines

Table 35.1 **Impact of antiviral vaccines on disease frequency: pre-vaccination era vs. 1998 (USA)**

		Annual reported cases:		
Disease	Dates	Pre-vaccination	Post-vaccination (1998)	Decrease (%)
Smallpox	1900–04	48,164	0	100
Poliomyelitis (paralysis)	1951–54	1,314	1*	100
Measles	1958–62	503,282	89	100
Mumps	1968	152,209	606	99.6
Rubella	1966–68	47,745	345	99.3
Congenital rubella syndrome	1958–62	823	5	99.4

**Single case of vaccine-associated paralytic poliomyelitis.*

From Morbidity and Mortality Weekly Report *1999*, **48**, *243–248*.

A brief history of antiviral vaccines

- 429 BC, Thucydides observes that people who survives smallpox in Athens does not become re-infected.
- 900 AD, Chinese discover a primitive form of vaccination

  - Powdered smallpox scabs are administered intranasally
- 1700s, Lady Montagu bring concept of variolation from Turkey to England

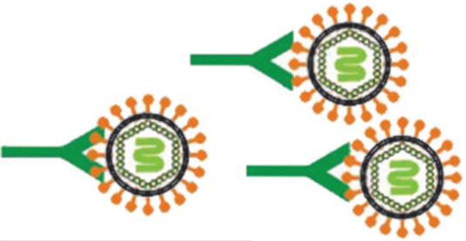
  - Inoculation with pus from recovering smallpox victim
- 1796, Edward Jenner discover vaccination

  - The use of cowpox inoculation to protect against smallpox
- 1880s, Louis Pasteur introduce air-dried rabbit spinal cord as rabies vaccine
- 1955, Salk develop inactivated Poliovirus vaccine
- 1980, WHO declare eradication of smallpox in the world

  - One of the most remarkable achievements in the history of medicine
- In the past 50 years, vaccination save more lives worldwide than any other medical product or procedure

A brief history of antiviral vaccines

- Technical advances supporting antiviral vaccine
  - 1850, Germans add glycerin to “cow lymph” to stabilize and decontaminate smallpox vaccine
  - 1879, Galtier succeeds in passaging rabies from rabbit to rabbit
  - 1885, Pasteur fix biological characteristics of rabies virus by passage in rabbit brains and discover that virulence in spinal cord is lost with drying
  - 1897, Loeffler and Frosch describe “filterable viruses” (foot-and-mouth disease virus)
  - 1931, Goodpasture first uses embryonated eggs to culture viruses
  - 1950, Enders, Weller, and Robbins launch systematic study of cell culture
  - 1953, Description of first immortalized cell line (HeLa)
  - 1960, Production of reassortant influenza A viruses in eggs
  - 1972, First DNA cloning performed
  - 1985, Hepatitis B surface antigen gene cloned and expressed in yeast



Types of antiviral vaccines

I. Live viruses

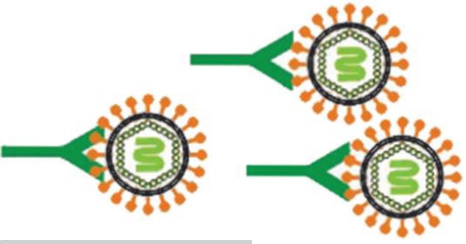
- **Wild-type viruses**: viruses may replicate poorly in non-natural host but share **immunogenic** determinants with related target viruses
- **Attenuated viruses**: serial passage and in vitro cultivation of viruses reduces their pathogenicity

II. Inactivated viruses

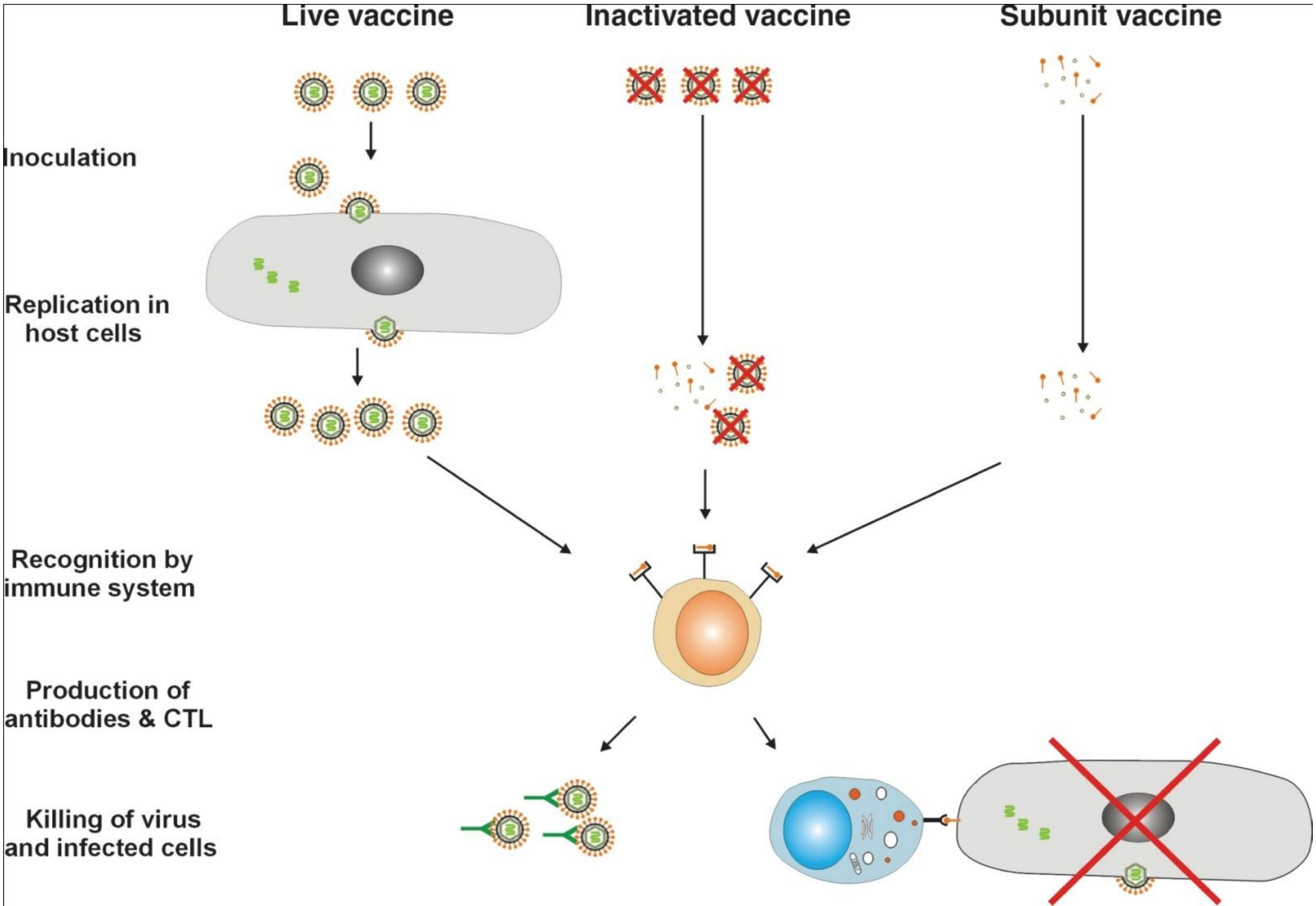
- Virus is grown, purified, and subjected to inactivation by treatment with chemicals or high temperatures

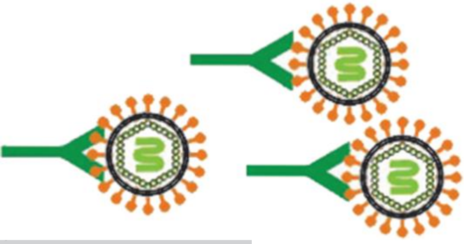
III. Subunit vaccines

- Consists of purified viral proteins that are immunogenic



Types of antiviral vaccines

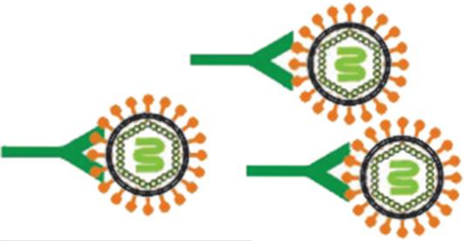




Current available human antiviral vaccines

Live wild-type viruses	Vaccinia (cowpox)[a]
Live attenuated viruses	Adenovirus[b]
	Influenza A (cold adapted)
	Measles
	Mumps
	Polio (Sabin)
	Rotavirus (human-recombinant)
	Rubella (german measles)
	Varicella (chickenpox)
	Yellow fever
Whole inactivated viruses	Hepatitis A
	Influenza A
	Influenza B
	Polio (Salk)
	Rabies
	Tick-borne encephalitis
Subunit vaccine	Hepatitis B surface antigen
Virus-like particles	Human papillomavirus
Chimeric virus	Rotavirus (human-bovine)

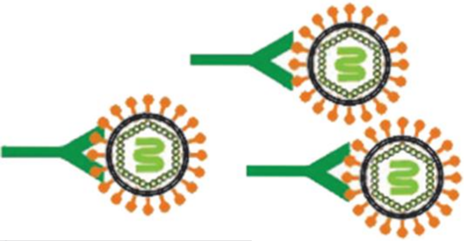
[a] *Smallpox eradicated (supply of vaccine tenuous).*
[b] *Military use only.*



Live viral vaccines

- <u>**Advantages**</u>
  - Single dose is sufficient; more effective and longer lasting immunity
  - Induce an immune response that comes closest to natural infection
  - Induce wide spectrum of immunoglobulin
  - Induce cell-mediated immunity
  - Economical and convenient

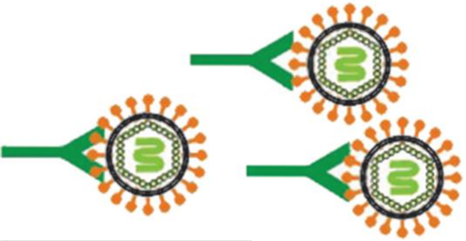
- <u>**Disadvantages**</u>
  - Can occasionally cause illness and death, especially in immunocompromised persons
  - Risk of reversion to virulence and contamination with dangerous virus
  - Heat labile, requiring attention to refrigeration via the cold chain
  - May be subject to inactivation by maternal antibodies when administered in early childhood



Inactivated whole virus vaccines

- **Advantages**
  - Stable, generally less sensitive to storage issues
  - Safer for the immunocompromised
  - No danger of virus spread

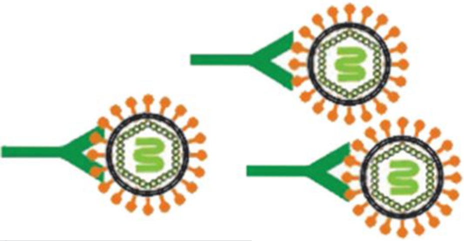
- **Disadvantages**
  - Expensive production
  - Must be injected and may require the addition of an adjuvant
  - Multiple injections are required
  - Less successful in inducing a robust immune response: no cell-mediated immunity



Subunit virus vaccines

- **<u>Advantages</u>**
  - Simplest and least expensive for production
  - Very stable
  - Safe in immunocompromised patients

- **<u>Disadvantages</u>**
  - Multiple doses and boosters are often required
  - May require an adjuvant
  - No cell-mediated immunity



How do antiviral vaccines work?

- The role of the immune system in fighting viral infections
  - **Cellular immune responses** mediate recovery from a majority of viral illnesses as those who lack humoral immune responses recover from most infections
    - Killing of infected cells via activated cytotoxic lymphocytes
  - **Neutralizing antibodies** can confer immunity to most pathogens

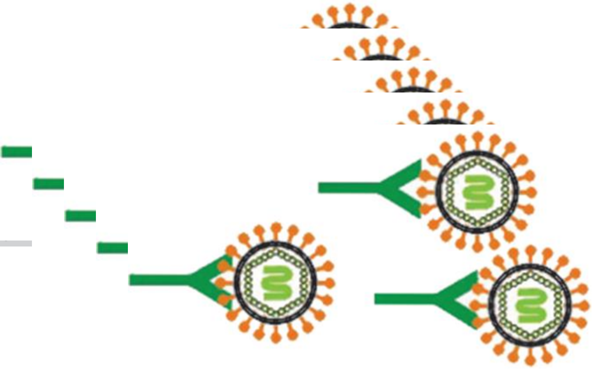
- Vaccines that stimulate cell-mediated immunity are being developed
  - Generation of antibodies may not be sufficient to control some viruses:

  ① Viruses that establish latent infections (herpesviruses)

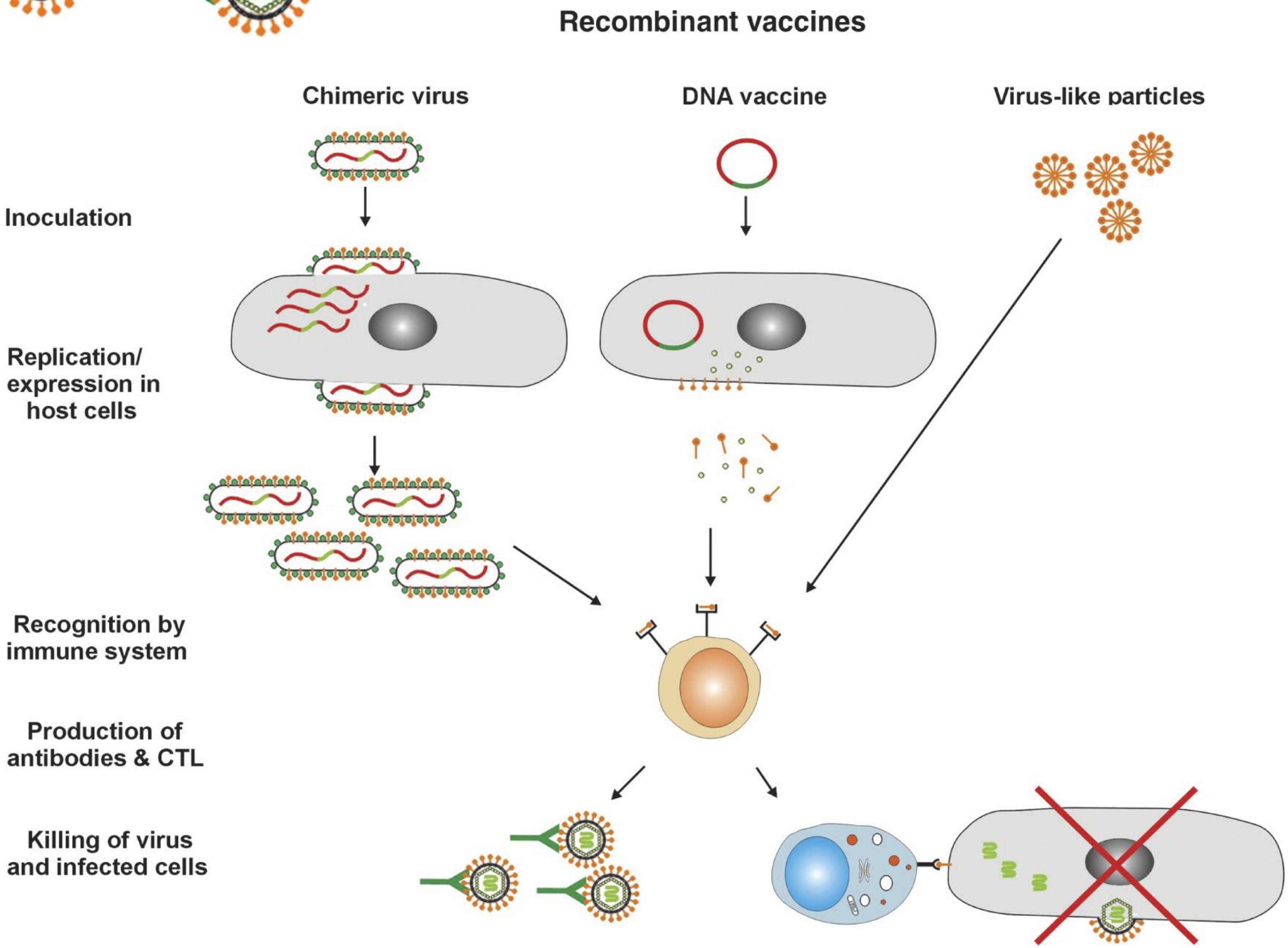
  ② Viruses with multiple serotypes and limited cross-neutralization (respiratory syncytial virus, dengue virus)

  ③ Rapidly mutating viruses (influenza A virus, HIV, HCV)

  ④ Viruses that establish chronic infections (HIV, HBV, HPV, herpesvirus)



New types of antiviral vaccines



New technologies for antiviral vaccines

A. New adjuvant systems

- **Oil-in-water emulsions** elicit strong humoral response without major toxicity
- **Cholera toxin B subunit** elicits strong humoral response without major toxicity
- **Toll-like receptor ligands** elicit strong humoral and cellular immune responses
  - CpG motifs: short, unmethylated DNA motifs that bind to TRL-9 and elicit potent, innate and cellular (Th-1-like) responses
  - Imiquimod/resiquimod: TLR-2 ligand that elicits strong humoral and cellular responses
  - Detoxified LPS: TLR-4 ligand that mimics bacterial infection and stimulates strong humoral and cellular responses
- **Pulsed dendritic cells**: Presentation of antigens to dendritic cells outside of the body and their reintroduction can lead to enhanced response to antigens
- **Conjugates**: A variety of molecules such as cytokines, monoclonal antibodies, and lectins can be conjugated to antigens to enhance immune reactions

New technologies for antiviral vaccines

B. Delivery systems

- **Liposomes**: Antigens are trapped inside vesicles made from synthetic lipids, enhancing immune reactions. Major problems with stability and consistency
- **Immune stimulating complexes (ISCOM):** More complex liposomal preparations that retain the capacity to elicit strong immune responses, but are more stable
- **Proteosomes**: Auto-assembling vesicles containing bacterial outer membrane proteins from Neisseria that can trap antigens and promote strong humoral and cellular responses
- **Plasmid DNA**: An expression plasmid containing the gene that encodes a viral antigen is introduced into the body. Expression of this gene in vivo can lead to potent induction of both humoral and cellular responses

New technologies for antiviral vaccines

B. Delivery systems (continued)

- **Viral or bacterial vectors**: Genes that encode viral antigens of interest can be inserted into non-pathogenic viral vectors (avian poxviruses, Semliki Forest virus) or bacterial vectors (attenuated Salmonella typhi) that retain some useful characteristics of the vector organisms (binding and entry, tissue tropism)
- **Virus-like particles**: Viral proteins, alone or in combination, that can either spontaneously self assemble or be coaxed into assembling with lipids to form nanoparticles resembling viruses

New technologies for antiviral vaccines

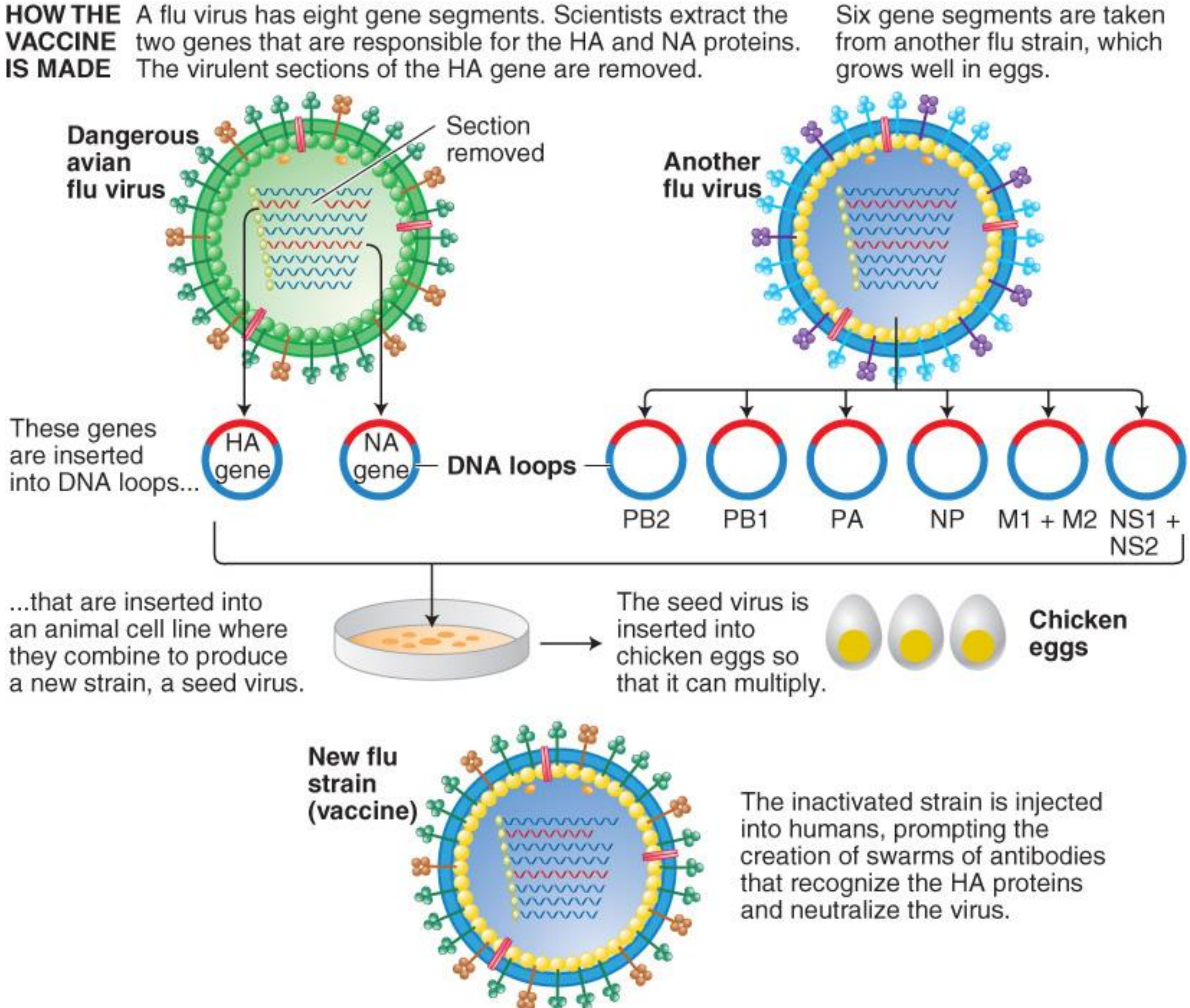
C. Delivery technologies

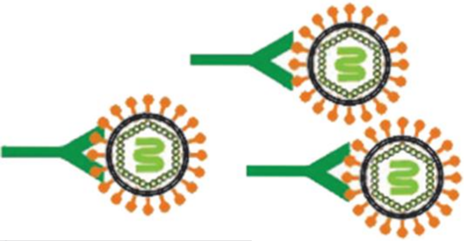
- **Aerosol**: a variety of ingenious mechanical devices are being studied for aerosolization of antiviral vaccine preparations for delivery either to the nasal or the lower respiratory mucosa
- **Eye drops, troches, suppositories**: formulation that deliver vaccine antigens to conjunctival, vaginal, or gastrointestinal mucosae
- **Foods**: Genetic manipulation of plants has made it possible to consider the delivery of viral and other antigens in foods such as bananas
- **Gene gun** accelerates gold particles carrying plasmid DNA to high velocities for penetration of skin to the desired depth, targeting dermal layers or muscle

New approaches in antiviral vaccines

- Vaccination with defined proteins
  - May reduce vaccine-adverse reactions
- Use of live viruses with defined attenuation characteristics
- Use of live vectors and chimeric viruses
  - Chimeric vaccine for rabies being used to control a major epizootic in raccoons
- Vaccines that can break **tolerance**
  - DNA vaccination, pulsed dendritic cell vaccination, and potent Th1-biasing adjuvants
- The changing vaccine paradigm
  - Viruses that have limited capacity to do harm are being targeted
  - Ubiquitous and persistent viruses are being targeted

Preparing a pandemic influenza vaccine using reverse genetics technology





New antiviral vaccines under development

Table 35.8 Some antiviral vaccines currently under development

Virus family	Virus species	Most promising strategies
Arenavirus	Junin	Live attenuated
	Lassa fever	Recombinant vaccinia virus
Calicivirus	Norwalk	Recombinant capsid "ghosts"
Filovirus	Ebola/Marburg	DNA
		Recombinant vesicular stomatitis virus
Flavivirus	Hepatitis C	Recombinant envelope glycoprotein, peptide, polypeptide
	Dengue	Tetravalent attenuated, DNA
Hepadnavirus	Hepatitis B	DNA, recombinant surface antigen including pre-S1/S2 regions; curative hepatitis B vaccine: DNA with CpG motifs
Herpesvirus	Epstein–Barr	Whole inactivated, subunit (gp350)
	Herpes simplex 1, 2	Recombinant polypeptide, vectored
Orthomyxovirus	Influenza A	Vectored, DNA, peptide
Paramyxovirus	Measles	Vectored, DNA
	Parainfluenza	Live attenuated
	Respiratory syncytial	Subunit G and fusion protein, DNA, vectored, peptide
Parvovirus	Parvovirus B19	Empty capsid with VP1 protein
Picornavirus	Enterovirus 71	Whole inactivated
Reovirus	Rotavirus	Live reassortants of simian or human origin
Retrovirus	HIV-1, 2	Recombinant polypetide, DNA, vectored, chimeric
Unclassified	Hepatitis E	Recombinant protein ORF2

Adverse events and ethical issues

- Ethical issues in the use of antiviral vaccines
  - **Herd immunity** can offer protection to those individuals who are not vaccinated, or for whom vaccination has failed
  - For those who refuse vaccination, managing their care if they get infected, and preventing them from spreading the virus to others is a controversial matter

Table 35.9 Severe adverse events associated with antiviral vaccine administration

Vaccine implicated	Event
Smallpox ("lymph" vaccines)	Sepsis due to bacterial contamination
Yellow fever (1942)	Vaccine lot contaminated with hepatitis B virus, leading to 28,000 cases of hepatitis B
Inactivated polio (1955)	Incomplete inactivation of virus, leading to 204 cases of paralytic disease (Cutter incident)
Inactivated measles (1960s)	Atypical (severe) disease upon exposure to natural measles infection
Attenuated polio (Sabin)	Vaccine-associated paralysis (~1 per 2.4 million persons vaccinated) due to reversion to more pathogenic strain
Live vaccines (vaccinia, polio, measles)	Dissemination and death in immunocompromised individuals
Attenuated live measles	Unexplained mortality in girls who received high titer formulations (relative risk of death doubled to age 5); more than 20 million doses of vaccine distributed
Inactivated influenza A	Apparent risk of Guillain Barré Syndrome (~1 per 1 million persons vaccinated), only in some years
Rotavirus (1999)	Intussusception—bowel folding and obstruction (vaccine withdrawn)