

## **VACCINES:**

- **attenuated viruses**
- **inactivated viruses**
- **purified viral components (subunit vaccines)**

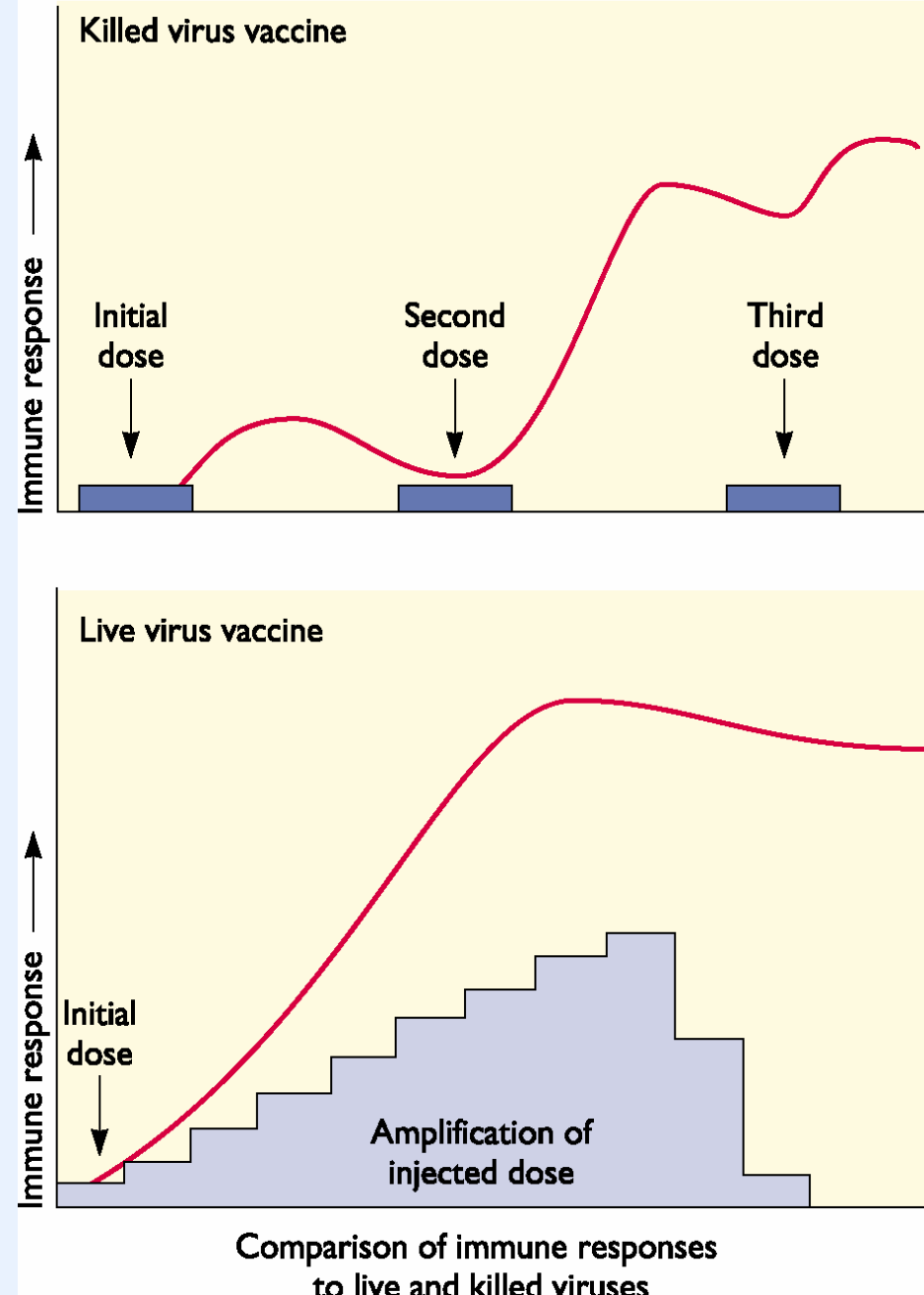
**Immune memory** Presence of specifically dedicated T and B lymphocytes that remain after an infection and maintain a heightened ability to respond to subsequent infection

**An effective vaccine** induces and maintains specific concentrations of antibodies (products of B cells) in serum and in points of viral entry. At the same time T cells responsible for specific cellular immunity are maintained in a precursor state ready to make their lethal products.

## Active immunization

employs a modified form of the virus and induces resistance to disease

**Passive immunization** the products of the immune response are introduced directly into the patient (Hepatitis A infection in 1997)



**Table 19.2** Viral vaccines licensed in the United States<sup>a</sup>

Disease or virus	Type of vaccine	Indications for use	Schedule
Hepatitis A	Inactivated whole virus	Travellers, other high-risk groups	0, 1, and 6 mo
Polio (inactivated)	Inactivated whole viruses of types 1, 2, and 3	Universal vaccination of infants	2, 4, and 12–18 mo of age; then 4–6 yr
Polio (live)	Live attenuated oral mixture of types 1, 2, and 3	Universal vaccination	2, 4, and 6–18 mo of age
Yellow fever	Live attenuated	Travel in areas where infection is common	One dose every 10 yr
Rubella	Live attenuated	Universal vaccination of infants	Same as measles, given as MMR <sup>b</sup>
Japanese encephalitis	Inactivated whole virus	Travelers or inhabitants of high-risk areas in Asia	0, 7, and 30 days
Influenza	Inactivated, viral subunits	Elderly and other high-risk groups	Two-dose primary series, then one seasonal dose
Measles	Live attenuated	Universal vaccination of infants	12 mo of age; 2nd dose, 6–12 yr of age
Mumps	Live attenuated	Universal vaccination of infants	Same as measles, given as MMR
Rabies	Inactivated whole virus	Exposure to rabies, actual or prospective	0, 3, 7, 14, and 28 days postexposure
Hepatitis B	Yeast-produced recombinant surface protein	Universal in children, exposure to blood, sexual promiscuity	0, 1, 6, and 12 mo
Adenovirus	Live attenuated oral	Military recruits	One dose
Varicella	Live attenuated	Universal vaccination of infants	12–18 mo of age
Smallpox	Live vaccinia virus	Certain laboratory workers	One dose

<sup>a</sup>Adapted from D. D. Richman et al., *Clinical Virology* (Churchill Livingstone, New York, N.Y., 1997), with permission.<sup>b</sup>MMR, measles-mumps-rubella.

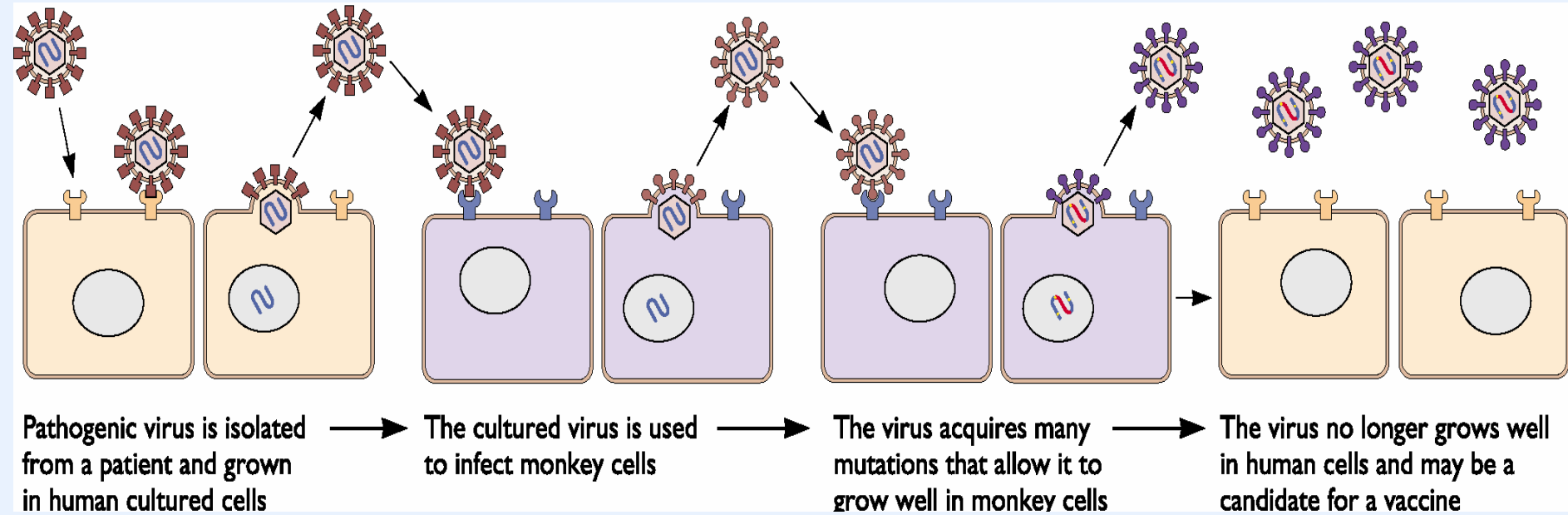
## **PREREQUISITES FOR VACCINES:**

- **Vaccines must be safe, efficacious and practical**
- **Vaccines containing inactivated virus or viral proteins must be free of infectious virus or contaminating nucleic acid**
- **Live attenuated vaccines must not revert to virulence**
- **Contamination of vaccines with adventitious agents introduced during production must be avoided**
- **Immunopathology induced in response to the vaccine**
- **Vaccine must induce protective immunity in the population as a whole**
- **Protection provided by a vaccine must be long term**
- **Stable, easy to administer and low cost**

## **LIVE ATTENUATED VACCINES:**

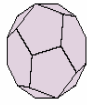
- **Virulent viruses can be made less virulent (attenuated) by growing them in cells other than the normal host or by propagating them at nonphysiological temperatures**
- **Live oral poliovirus vaccine comprises three attenuated strains selected for their reduced neurovirulence**
- **Live measles virus vaccine contains attenuated viruses isolated from serial passages through human kidney, human amnion, sheep kidney and chick embryo cells**
- **Attenuated viruses grown in tissue culture cells can be contaminated with viruses resident in these cells**
- **Alternatives include recombinant DNA technology; virulence genes can be isolated and attenuated by deletion or by mutagenesis**
- **Recombinant DNA methods allow cloning of appropriate viral genes into nonpathogenic viruses, bacteria, insect cells or plants**
- **Since only a portion of the viral genome is used in these systems, there can be no contamination of the resulting vaccine with the original virus**

# Attenuation of viruses by passage in nonhuman cells:



# Polio vaccine

## A Derivation of Sabin type 3 attenuated poliovirus



Type 3  
P3/Leon/37  
(isolate from fatal paralytic case)



Passages

21 passages in vivo (intracerebrally in monkeys)  
8 passages in vitro (monkey testicle cultures)  
39 passages in vitro (monkey kidney cultures)  
3 plaque purifications (monkey kidney cultures)  
3 passages in vitro (preparative, monkey kidney cultures)



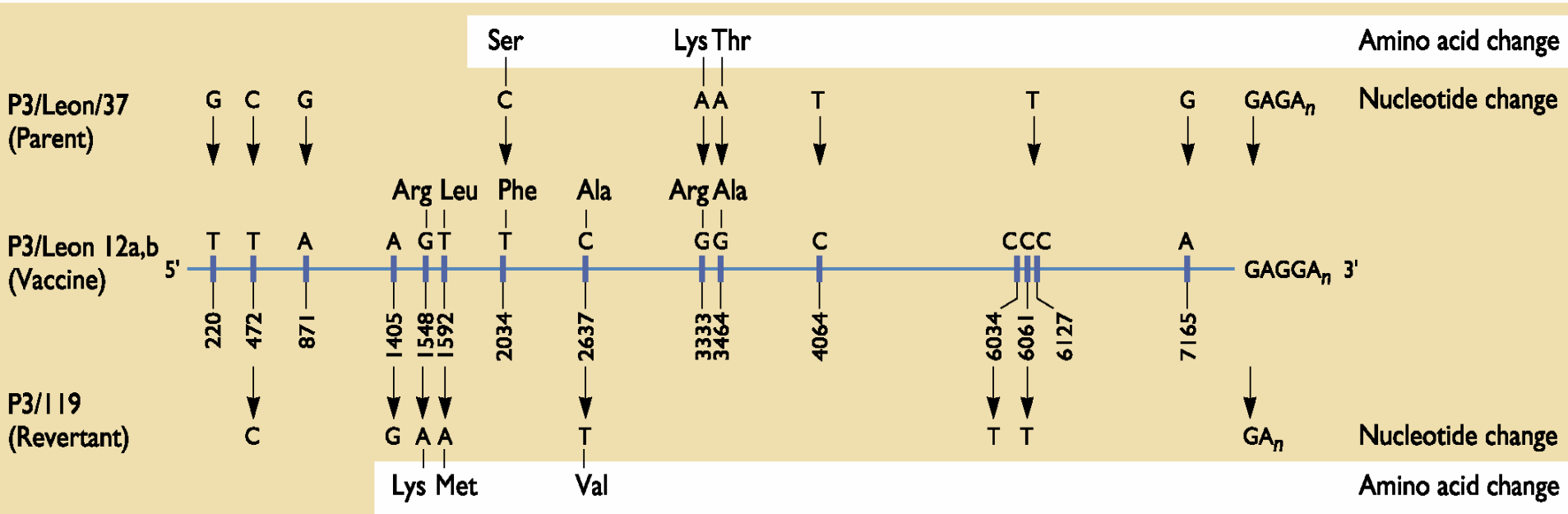
P3/Leon 12a1b KP3/56 Sabin vaccine strain

## B Determinants of attenuation in the Sabin vaccine strains

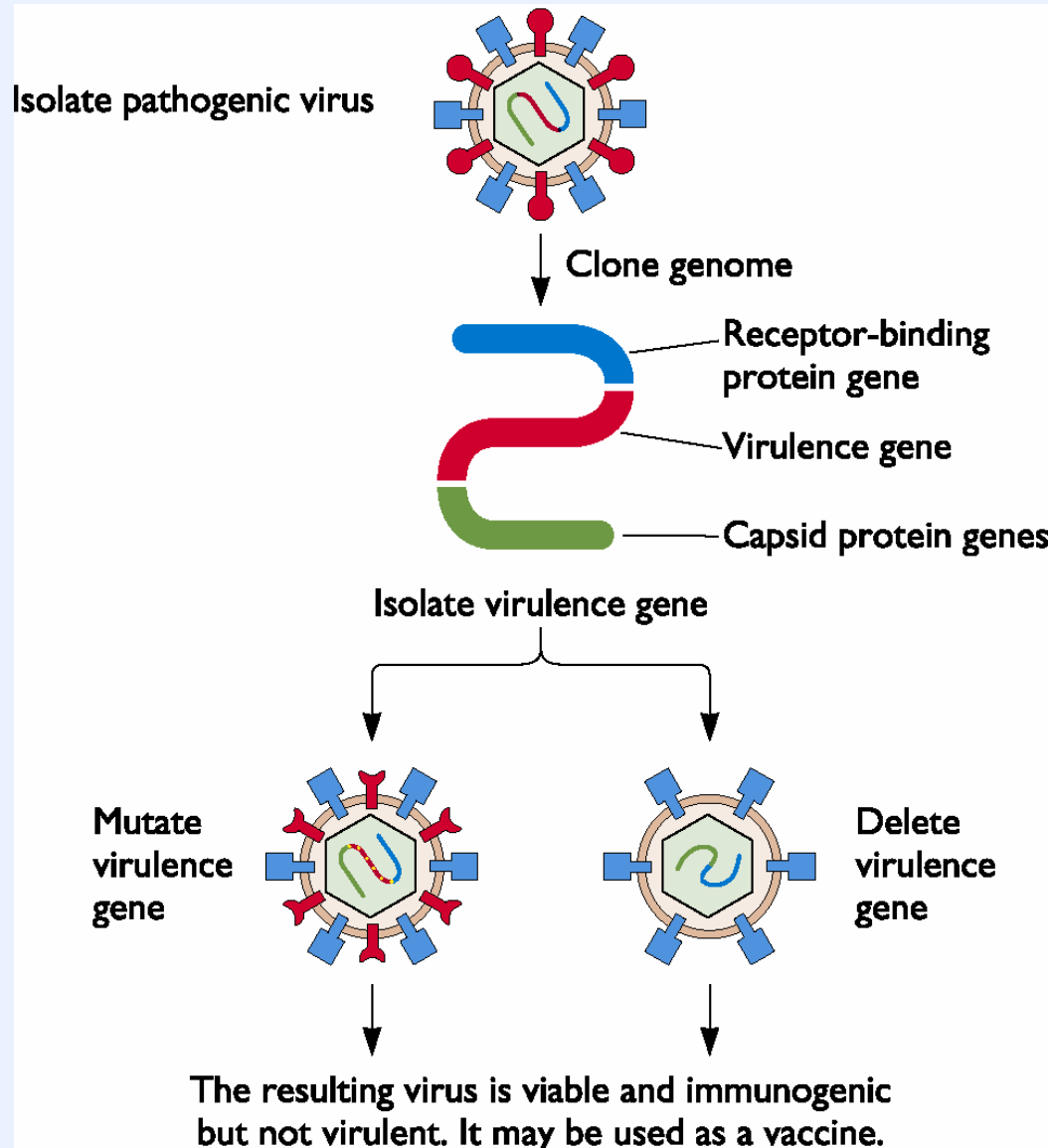
Virus	Mutation (location/nucleotide position)
P1/Sabin	5'-UTR (480) VP1 (1106) VP1 (1134) VP3 (3225) VP4 (4065)
P2/Sabin	5'-UTR (481) VP1 (1143)
P3/Sabin	5'-UTR (472) VP3 (3091)

# Differences in the nucleotide sequences of the virulent P3/leon strain and the attenuated P3/Sabin vaccine strain:

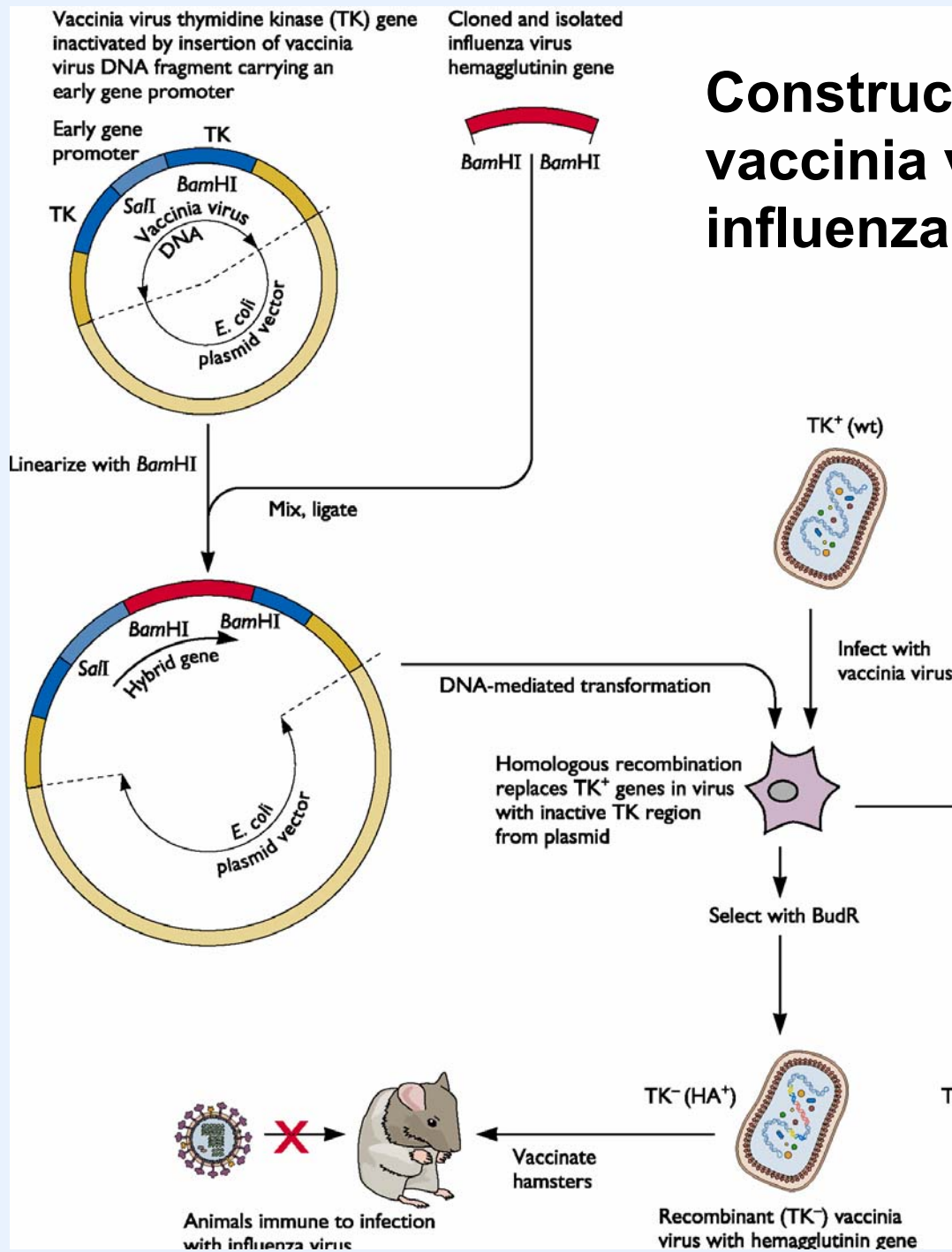
## C Reversion of P3/Sabin



# Construction of attenuated viruses using recombinant DNA technology:



# Construction of an infectious vaccinia virus expressing the influenza virus HA gene



# NEW VACCINE TECHNOLOGY

## Viral vectors:

- A nonpathogenic virus can be used to immunize the host against a pathogenic virus by constructing a virus that can present the pathogenic viral proteins to the immune system
- Vaccinia virus provided the foundation of the vaccine program for eradicating smallpox, it continues to serve as a unique viral vector for production of foreign proteins in mammalian cells
- Host is immunized against the viral vector, as well as the viral antigen. Subsequent uses of the same vector may result in a weak response, no response or an immunopathological response.
- Introducing viral vectors into a population may have long term effects, such as in immunocompromised individuals

## **DNA VACCINES:**

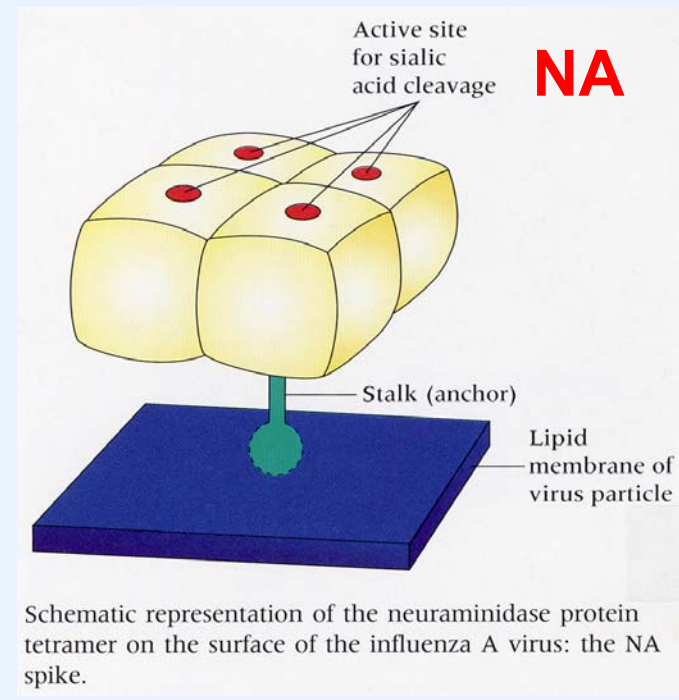
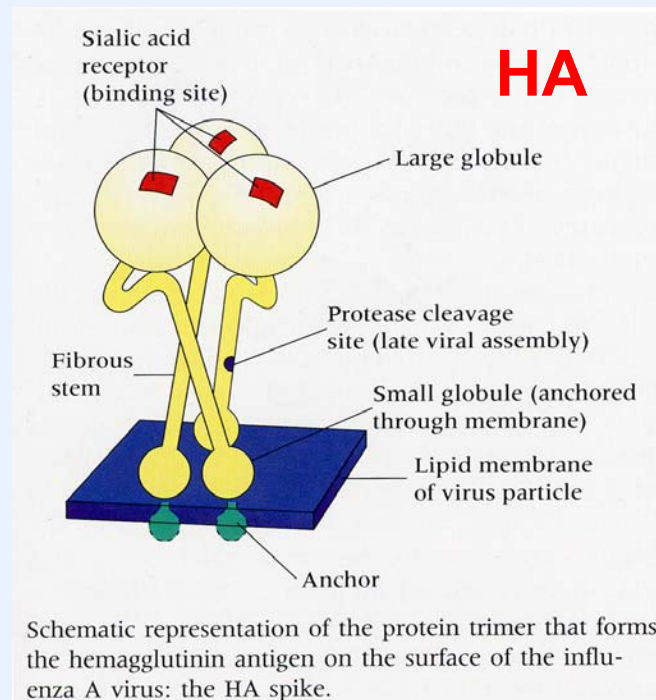
- **In 1992, a variation of the subunit vaccine approach was introduced. In this case vaccine was not a protein, but naked DNA consisting of a plasmid that can be expressed inside a cell.**
- **No adjuvants or special formulations are necessary to stimulate the immune response.**
- **An immune response is produced by injection into muscle or skin of a few micrograms of plasmid DNA encoding the immunogenic protein.**
- **Another method of delivery is the gene gun that shoots DNA through the skin to introduce the plasmid into dermal tissue.**
- **Possible dangers are integration of plasmid DNA leading to insertional mutagenesis, induction of antiDNA antibodies and induction of immune tolerance.**

# Influenza Subunit Vaccine

- **Antigens decided on in February each Year.**
- **Takes six months to produce.**
- **Made from egg-grown viruses; Virus extracted and inactivated. Then HA and NM subunits recovered.**
- **Contains antigens from two Influenza A viruses & one Influenza B virus that are predicted to circulate in the upcoming winter**
- **Should be administered in October or November**
- **Antibodies reach protective levels 2 weeks after vaccination.**
- **Annual vaccination is necessary even if one or more of the antigens are unchanged from the previous year because immunity declines in the year following vaccination.**

# Influenza A Isolates Vary in HA & NA Antigenic Determinants

HA & NA variation has major role in evolution of strains causing epidemics. Fifteen HA & nine NA antigenic variants known. Combinations of the two surface proteins result in evolution of new strains that can evade antibodies from previous flu infections.



# Influenza Strains Evolve by **Antigenic Shift** & **Antigenic Drift**

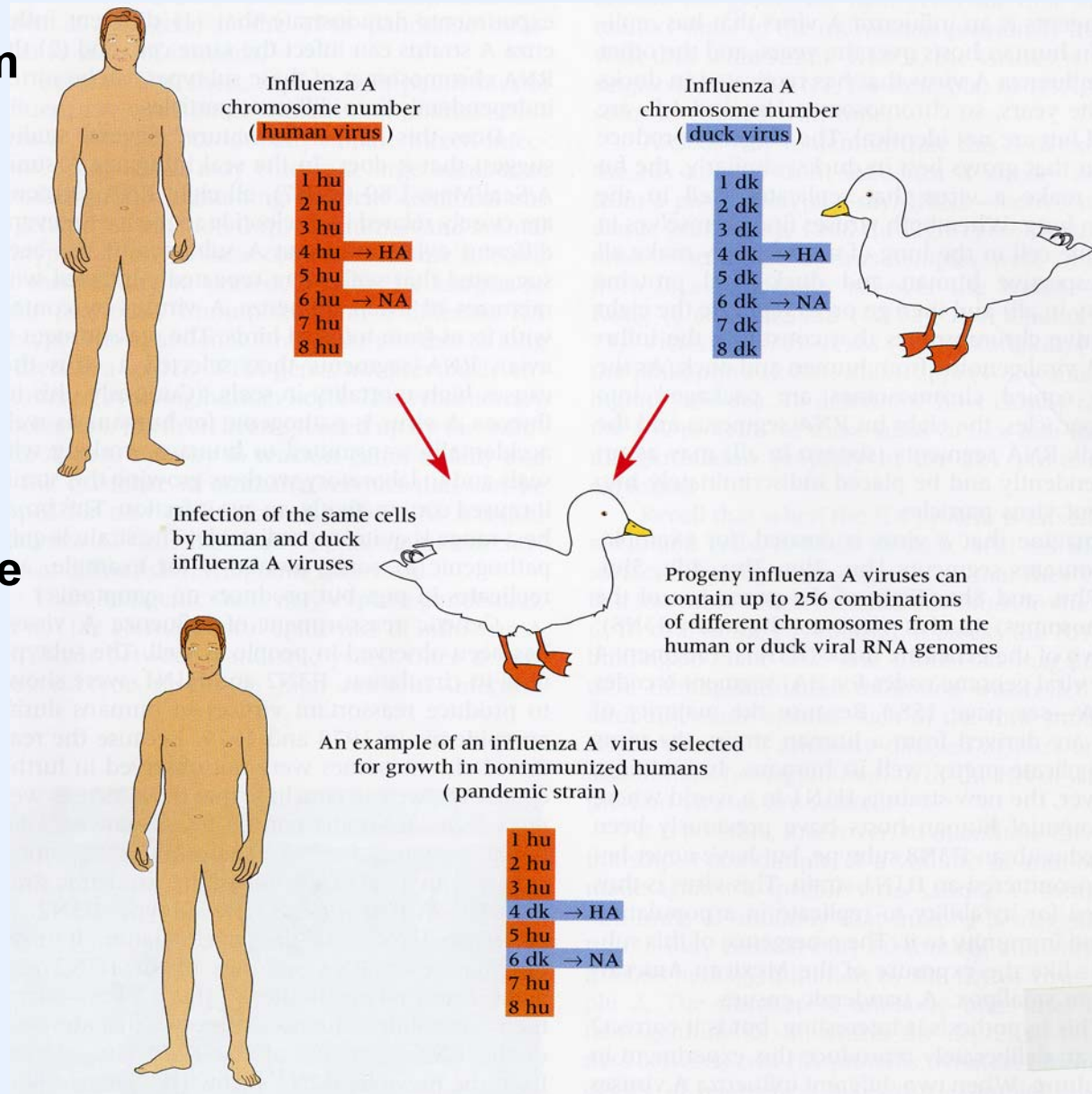
**Antigenic Shifts** result from **Genome Reassortment** in birds or mammals during **double Infection** by **Two** strains of influenza.

**Increased virulence** can result from **reassortment** of any of the segments.

**However**, strains capable of **evading host immune surveillance** usually require changes in **HA** and **NA** antigenic determinants.

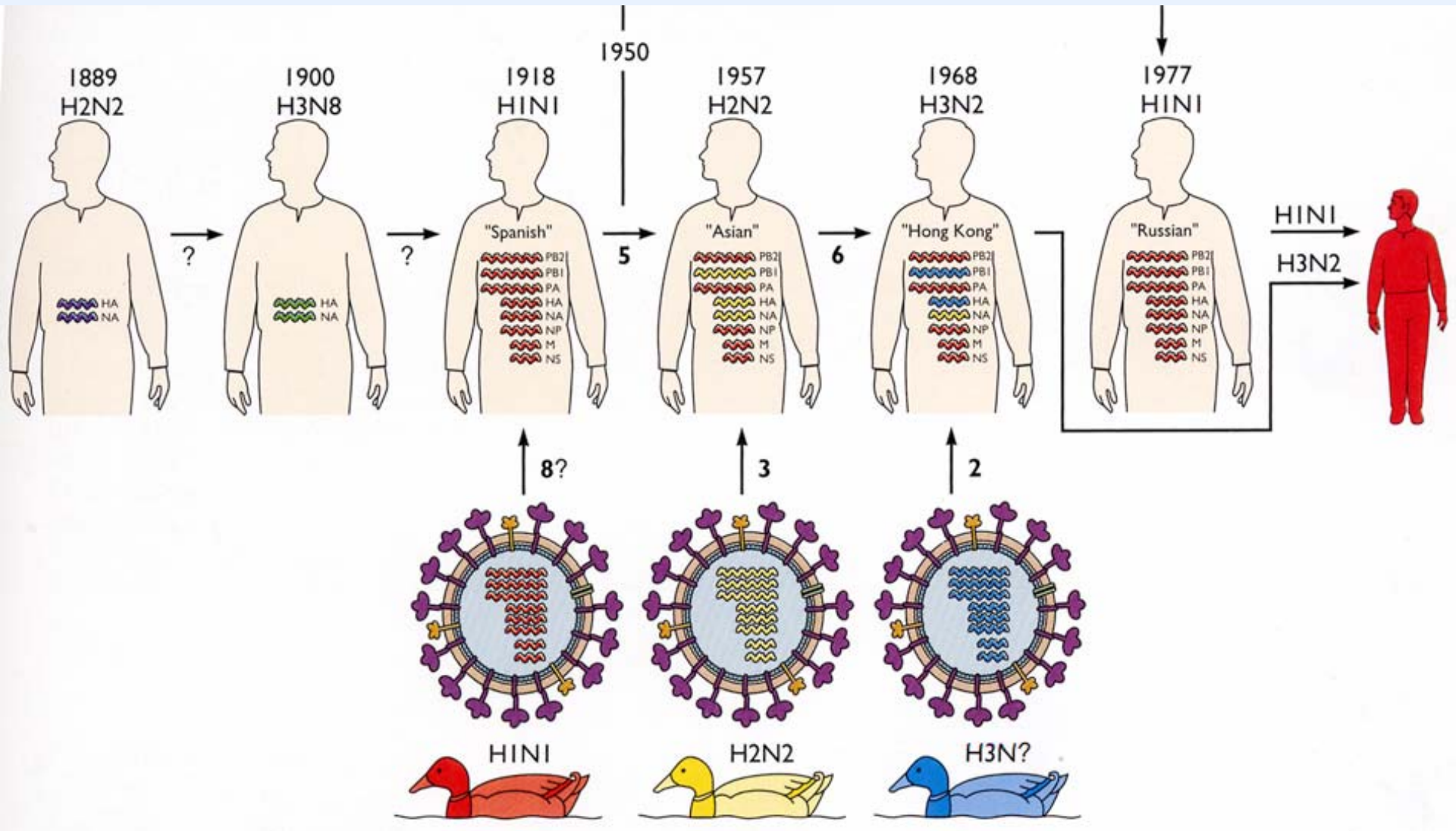
**Genomic Reassortment** leads to very **rapid virus strain evolution**.

**Antigenic Drift** arises from simple amino acid mutations within **HA** & **NA**. **Antigenic Drift** is a **slow process**.



**Genome Reassortment or Antigenic Shift**

# HN & NM Composition of Isolates Causing Pandemics



**Pandemic Strains Originated by "Antigenic Shifts"**

# Influenza Vaccine Antigens, 1994-2004

	<b>A H3N2</b>	<b>A H1N1</b>	<b>B</b>	
<b>1994-95</b>	<b>Shangdong/09/93</b>	<b>Texas/36/91</b>	<b>Panama/45/90</b>	
<b>1995-96</b>	<b>Johannesburg/22/94</b>		<b>Harbin/07/94</b>	
<b>1996-97</b>	<b>Nanchang/933/95</b>			
<b>1997-98</b>		<b>Johannesburg/82/96</b>	<b>Beijing/184/93</b>	
<b>1998-99</b>	<b>A/Sydney/5/97</b>	<b>A/Beijing/262/95</b>		
<b>1999-00</b>				
<b>2000-01</b>	<b>Moscow/10/99</b>	<b>New Caledonia/20/99</b>	<b>Sichuan/379/99</b>	
<b>2001-02</b>				
<b>2002-03</b>			<b>Fujian</b>	<b>Hong Kong/330/01</b>
<b>2003-04</b>				
<b>2004-05</b>				

# Efficacy of Influenza Vaccine

<b>Group</b>	<b>Outcome Prevented</b>	<b>Efficacy</b>
healthy <65 years old	Illness due to influenza	70-90%
Elderly in nursing homes	Illness due to influenza	30-40%
Elderly in nursing homes	Hospitalization & pneumonia	50-60%
Elderly in nursing homes	Death	80%

## Determinants of Vaccine Efficacy:

- **Closeness of match between circulating virus & vaccine strains.**
- **Age of the Patents.**
- **MMWR 1000-67/PP/01/1 Immunocompetence of the Patents.**

This could be  
you....

Get your flu  
shot!!!

