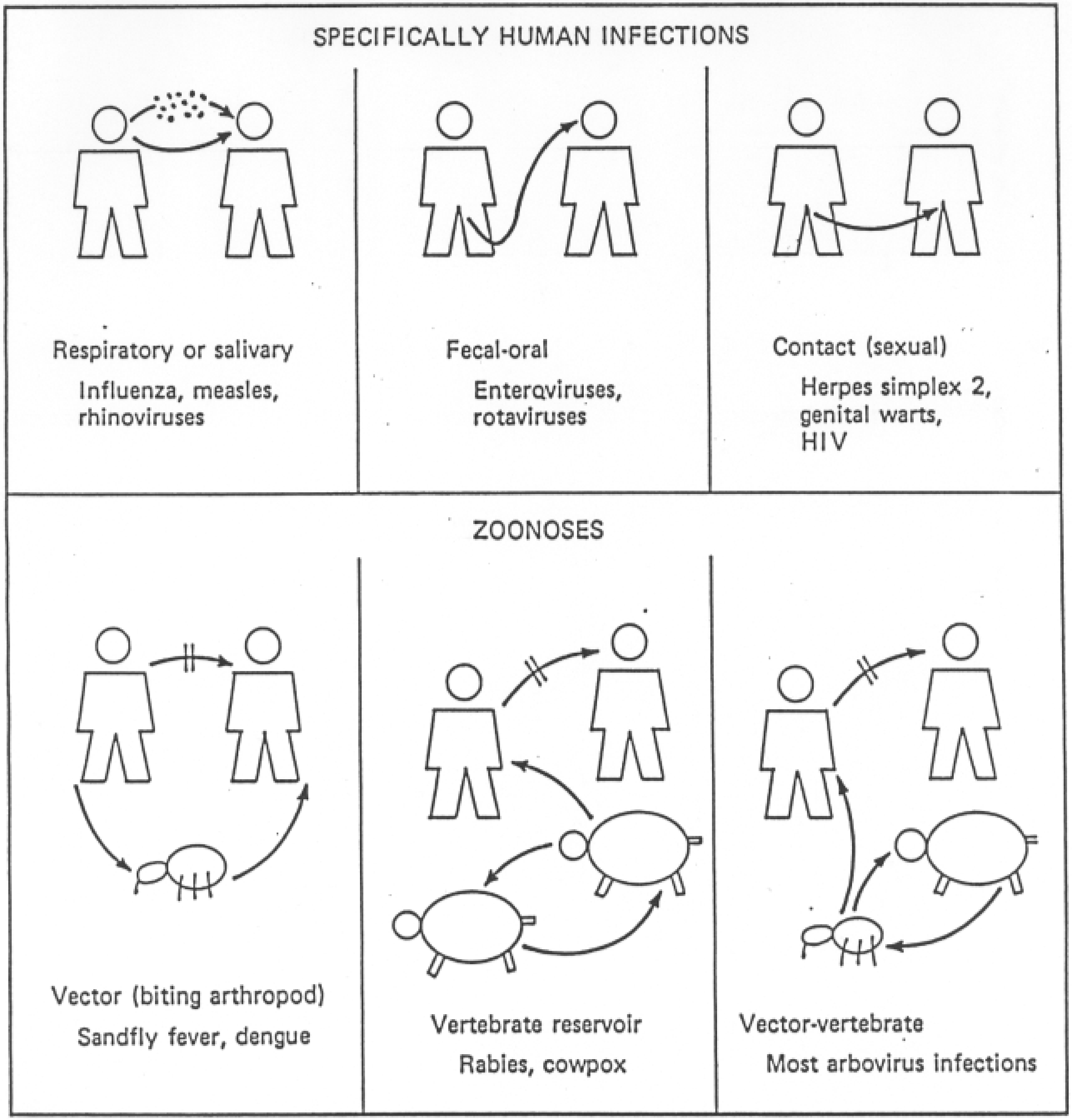
Control of Viral infections

Preventative measures

- Quarantine
- Hygiene
- Vector control
- Changes in lifestyle
- Vaccines

Viruses limited to humans much easier to control



What makes a good vaccine?

BOX 15–1. Properties of a Good Candidate for Vaccine Development

Organism causes significant illness.
Organism exists as only one serotype.
Antibody blocks infection or systemic spread.
Organism does not have oncogenic potential.
Vaccine is heat-stable so that it can be transported to endemic areas.

BOX 15–2. Problems with Vaccine Use

Live vaccine can occasionally revert to virulent forms.
Interference by other organisms may prevent the infection produced by a live virus vaccine; for example, rubella prevents replication of polio virus.
Vaccination of an immunocompromised person with a live vaccine can be life-threatening.
Side effects to vaccination can occur; these include hypersensitivity and allergic reactions to the antigen, to nonmicrobial material in the vaccine, and to contaminants (e.g., eggs).
Vaccine development and liability insurance for the manufacturer are very expensive.
Organisms with many serotypes are difficult to control with vaccination.

From Murray et. al., Medical Microbiology 5th edition, 2005, Chapter 15, published by Mosby Philadelphia,,

Vaccines – live or killed?

TABLE 15–2. Advantages and Disadvantages of Live Versus Inactivated Vaccines

Property	Live	Inactivated
Route of administration	Natural[a] or injection	Injection
Dose of virus, cost	Low	High
Number of doses	Single[b]	Multiple
Need for adjuvant	No	Yes[c]
Duration of immunity	Long-term	Short-term
Antibody response	IgG, IgA[d]	IgG
Cell-mediated immune response	Good	Poor
Heat lability in tropics	Yes[e]	No
Interference[f]	Occasional	None
Side effects	Occasional mild symptoms[g]	Occasional sore arm
Reversion to virulence	Rarely	None

From Murray et. al., Medical Microbiology 4th edition, 2004, Chapter 15, published by Mosby Philadelphia,,

Status of Viral Vaccines (live and inactivated)

TABLE 15–4. Viral Vaccines*

Virus	Vaccine Components	Who Should Receive Vaccinations
Polio	Inactivated (IPV, Salk vaccine)	Children
	Attenuated (oral polio vaccine, Sabin vaccine)	Children
Measles	Attenuated	Children
Mumps	Attenuated	Children
Rubella	Attenuated	Children
Varicella-zoster	Attenuated	Children
Influenza	Inactivated	Adults, especially medical personnel and the elderly
Hepatitis B	Subunit	Newborns, health care workers, high-risk groups (e.g., promiscuous people, intravenous drug users)
Hepatitis A	Inactivated Live (China)	Children, child-care workers, travelers to endemic areas, Native Americans and Alaskans
Adenovirus	Attenuated	Military personnel
Yellow fever	Attenuated	Travelers at risk to exposure, military personnel
Rabies	Inactivated	Anyone exposed to virus Preexposure: veterinarians, animal handlers
Rotavirus	Rhesus/bovine/human hybrids	In development
Smallpox	Live vaccinia virus	No longer necessary
Japanese encephalitis	Inactivated	Travelers at risk to exposure
Eastern, Western, Russian spring-summer encephalitis viruses	Inactivated	Military personnel

From Murray et. al., Medical Microbiology 4th edition, 2002, Chapter 15, published by Mosby Philadelphia,,

The principles of DNA based vaccines

Functional components of DNA vaccine plasmid

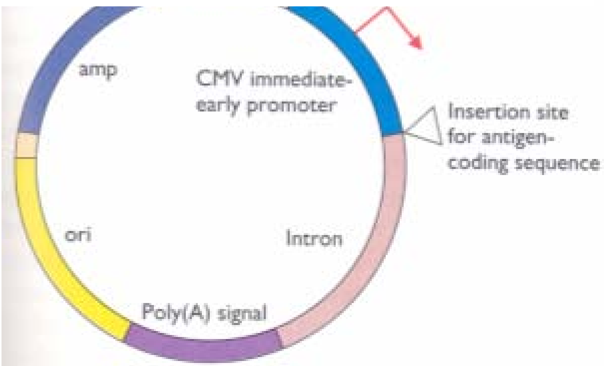


Figure 19.11 Functional components of a DNA vaccine expression vector. The system is based on a double-stranded plasmid, typically from *E. coli*, carrying its own origin of replication (ori) and a selectable marker (amp [ampicillin resistance]). A key component is a strong eukaryotic promoter element (here it is the major immediate-early promoter from human cytomegalovirus [CMV]). The antigen-encoding gene is placed downstream of this strong promoter at an engineered insertion site. Expression of the antigen may be enhanced by including an intron sequence (to facilitate transport of mRNA from the nucleus) and a 3′ untranslated sequence that provides a polyadenylation signal as well as stability to the antigen-encoding mRNA.

Table 19.5 DNA vaccines in animal models[a]

Pathogen	Proteins	Induction of[b]: AB	CTL	Protection
Hepatitis C virus	Nucleocapsid	+	+	+
Influenza virus	NP, HA, M1	+	+	+
Rabies virus	Glycoprotein, NP	+	+	+
Lymphocytic choriomeningitis virus	NP	+	+	+
Human immunodeficiency virus	Env, Gag, Rev	+	+	ND
Human T-cell leukemia virus type 1	Env	+	ND	ND
Hepatitis B virus	Surface, core antigens	+	+	+
Bovine herpesvirus	Glycoprotein	+	ND	+
Herpes simplex virus	gB, gD, ICP27	+	+	+

[a]Adapted from J. B. Ulmer et al., *ASM News* **62**:476–479, 1996.

[b]ND, not detected; AB, antibody; CTL, cytotoxic T lymhocytes. "Protection" refers to survival after a lethal virus challenge.

Flint, Enquist, Krug, Racaniello and Skalka, "Principles of Virology" ASM press, 2000, chapter 19

The use of drugs (antivirals) to control virus infections

Box 50-1. Viruses Treatable with Antiviral Drugs

Herpes simplex virus
Varicella-zoster virus
Cytomegalovirus
Human immunodeficiency virus
Influenza A virus
Respiratory syncytial virus
Hepatitis A, B, and C viruses*
Papillomavirus*
Picornavirus

From Murray et. al., Medical Microbiology 5th edition, 2005, Chapter 50, published by Mosby Philadelphia,,

Potential targets for the design of antiviral drugs

Table 50-1 **Examples of Targets for Antiviral Drugs**

Replication Step or Target	Agent	Targeted Virus*
Attachment	Peptide analogues of attachment protein	Human immunodeficiency virus (gp 120/CD4 receptor)
	Neutralizing antibodies	Most viruses
	Dextran sulfate, heparin	Human immunodeficiency virus; herpes simplex virus
Penetration and uncoating	Amantadine, rimantadine	Influenza A virus
	Tromantadine	Herpes simplex virus
	Arildone, disoxaril, pleconaril	Picornaviruses
Transcription	Interferon	Hepatitis A, B, and C viruses; papillomavirus
	Antisense oligonucleotides	Papillomavirus
Protein synthesis	Interferon	Hepatitis A, B, and C viruses; papillomavirus
DNA replication (polymerase)	Nucleoside analogues	Herpesviruses; human immunodeficiency virus; hepatitis B virus
	Phosphonoformate, phosphonoacetic acid	Herpesviruses
Nucleoside biosynthesis	Ribavirin	Respiratory syncytial virus; Lassa fever virus
Nucleoside scavenging (thymidine kinase)	Nucleoside analogues	Herpes simplex virus; varicella-zoster virus
Glycoprotein processing	—	Human immunodeficiency virus
Assembly (protease)	Hydrophobic substrate analogues	Human immunodeficiency virus
Virion integrity	Nonoxynol-9	Human immunodeficiency virus; herpes simplex virus

*Therapies may not have received approval for human use.

From Murray et. al., Medical Microbiology 5th edition, 2005, Chapter 50, published by Mosby Philadelphia,,

FDA approved antiviral drugs

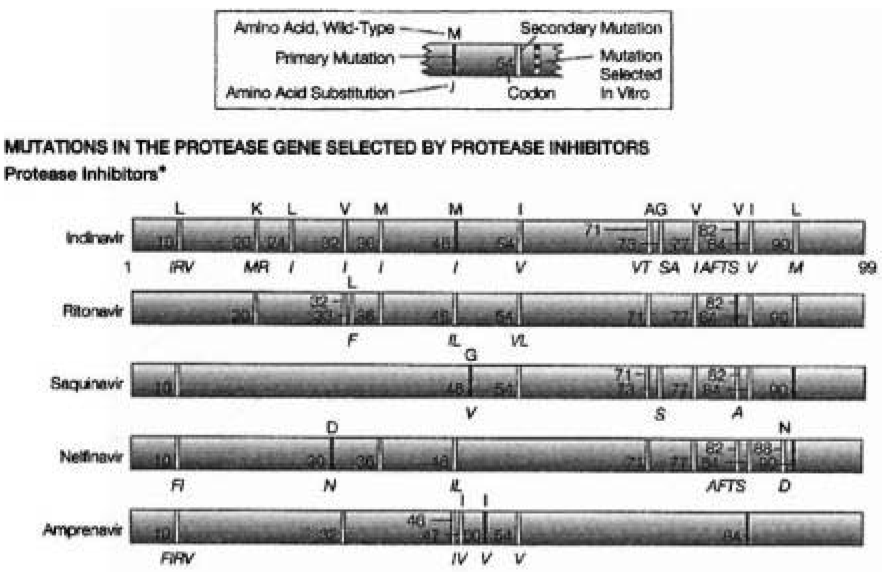
Table 50-2 **Antiviral Drug Therapies Approved by the U. S. Food and Drug Administration**

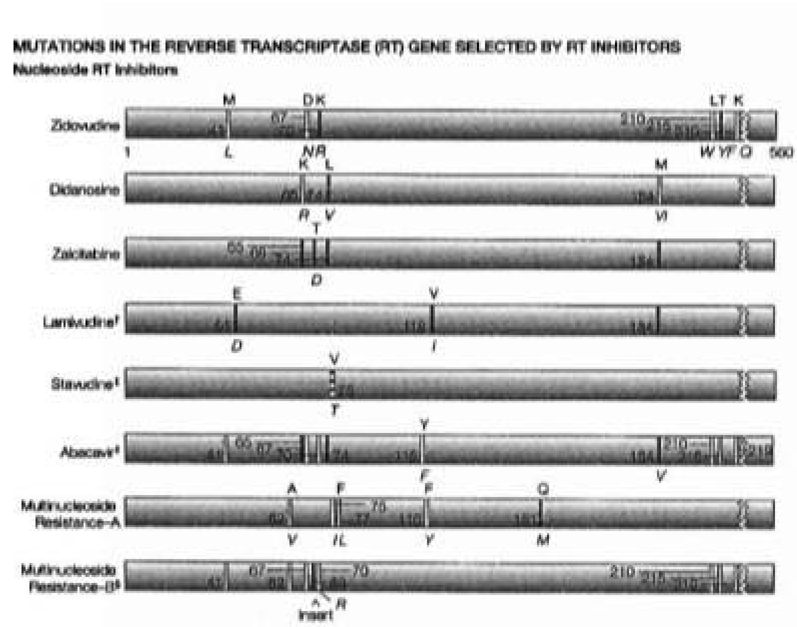
Virus	Antiviral Drug	Trade Name
Herpes simplex virus	Acyclovir*	Zovirax
	Penciclovir	Denavir
	Adenosine arabinoside (ara-A, vidarabine)	Vira-A
	Iododeoxyuridine (idoxuridine)†	Stoxil
Varicella-zoster virus and herpes simplex virus	Valacyclovir	Valtrex
	Famciclovir	Famvir
Cytomegalovirus	Ganciclovir	Cytovene
	Phosphonoformate (foscarnet)	Foscavir
Human immunodeficiency virus		
Nucleoside analogue reverse transcriptase inhibitors	Azidothymidine (zidovudine)	Retrovir
	Dideoxyinosine (didanosine)	Videx
	Dideoxycytidine (zalcitabine)	Hivid
	Stavudine (d4T)	Zerit
	Lamivudine (3TC)	Epivir
Non-nucleoside reverse transcriptase inhibitors	Nevirapine	Viramune
	Delaviridine	Rescriptor
Protease inhibitors	Saquinavir	Invirase
	Ritanavir	Norvir
	Indinavir	Crixivan
	Nelfinavir	Viracept
Influenza A virus	Amantadine	Symmetrel
	Rimantadine	
Influenza A and B viruses	Zanamivir	Relenza
	Oseltamivir	Tamiflu
Hepatitis C virus	Interferon α	Roferon-A (interferon α-2a)
		Intron A (interferon α-2b)
Papillomavirus	Interferon α	
Respiratory syncytial virus, Lassa virus	Ribavirin	Virazole
Picornaviruses	Pleconaril	

* Also active against varicella-zoster virus   ᵀ Topical use only

From Murray et. al., Medical Microbiology 5th edition, 2005, Chapter 50, published by Mosby Philadelphia,,

The use of antiviral drugs leads to resistant virus





Fields Virology 4th edition, 2002, Chapter 15, Lippincott, Williams and Wilkins, 2002

Bioterrorism - smallpox

Progression of smallpox rash/lesions

Day 1 Day 2 Day 3 Day 4

The rash appears 2 to 4 days after the patient first becomes ill with fever. On the first day of rash a few raised spots called papules appear. They are usually seen first on the face, and subsequently on the body and extremities. On the right side of this picture, a few small papules may be seen. Unless it is known that the patient has been exposed to the virus or in contact with a smallpox case two weeks before, one may not suspect the diagnosis at this time. On the second day of rash, more papules appear. Although they differ somewhat in size, note that they all have a very similar appearance. By day 3, the rash has become more distinct and raised above the skin surface. Fluid is accumulating in the papules to form vesicles. By day 4, the vesicles are more distinct. Although they contain fluid, they feel very firm to the touch. When broken, they do not collapse because the fluid is contained in many small compartments

Progression of smallpox rash/lesions

Day 5 | Day 7 | Day 8-9 | Day 10-14 | Day 20

By day 5, the fluid in the vesicles has become cloudy and looks like pus. At this stage, the pocks are called pustules. At this time, the fever usually rises and the patient feels more ill than before. On day 7, the rash is definitely pustular. Note that the pocks, although varying somewhat in size, all resemble each other in appearance. The rash is now so characteristic that there should be no mistake in diagnosis. During days 8 and 9, the pustules increase somewhat in size. They are firm to the touch and deeply embedded in the skin. Gradually the pustules dry up and dark scabs form. The scabs begin to appear between 10 and 14 days after the rash first develops. The scabs contain live smallpox virus. Until all scabs have fallen off, the patient may infect others. By day 20, the scabs have come off and light-coloured or depigmented areas are observed.
Over a period of many weeks the skin gradually returns to its normal appearance. However, scars which last for life may remain on the face. Such scars are an indication of previous infection with smallpox.

Distinguishing features of Smallpox from other rashes

Note in this slide that the density of the rash is greater on the face than on the body.

Pocks are usually present on the palms of the hands and on the soles of the feet.

Features of smallpox which facilitated eradication

- **Virology and Disease aspects**
  - No secondary hosts; human only virus
  - Long incubation period
  - Infectious only after incubation period
  - Low communicability
  - No persistent infection
  - Subclinical infections are not a source of spread
  - Easily diagnosed
  - Previous infected individuals obvious because of scarring
- **Immunology**
  - Infection confers long-term immunity
  - One stable serotype
  - Effective vaccine available
  - Vaccine is stable and cheap
- **Social-political aspects**
  - Severe disease with high morbidity and mortality
  - Considerable cost savings to developed, nonendemic countries
  - Eradication from developed countries demonstrated its feasibility
  - Few cultural or social barriers to case tracing and control

Comparison of properties of smallpox, measles and polio relevant to eradication

White and Fenner, "Medical Virology 4th edition, Academic Press, 1994 Chapter 15

Comparison of Features Influencing the Feasibility of Eradication of Measles and Poliomyelitis, Compared with Smallpox, in Which All Features Were Favorable

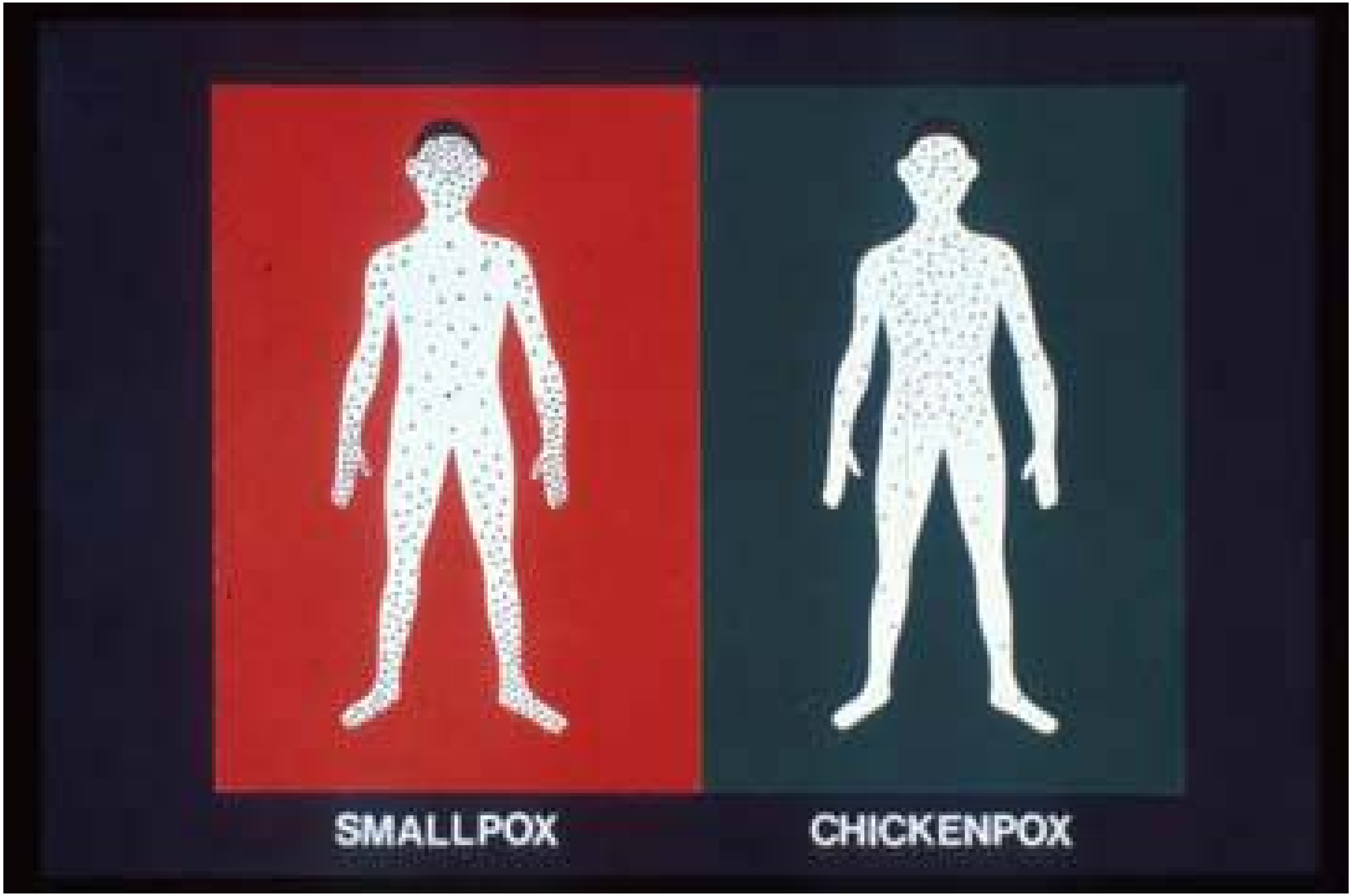
	Smallpox	Measles	Poliomyelitis
Biological features			
Reservoir host in wildlife	No	No	No
Persistent infection occurs	No	Yes[a]	No
Number of serotypes	1	1	3
Antigenically stable	Yes	Yes	Yes
Vaccine			
Effective	Yes	Yes[b]	Yes
Cold chain necessary	No	Yes	Yes
Number of doses	1	2	4
Infectivity in prodromal stage	No	Yes	Yes
Subclinical cases occur	No	No	Yes
Early containment possible	Yes	No	No
Sociopolitical features			
Country-wide elimination achieved	Yes[c]	No	Yes[d]
Financial incentive for assistance	Strong	Weak	Weak[e]
Records of vaccination required	No—scar	Yes	Yes

[a] As subacute sclerosing panencephalitis, but since no shedding occurs in this disease it is epidemiologically irrelevant.
[b] Vaccination is ineffective in the presence of maternal antibody.
[c] Before the Intensified Smallpox Eradication Programme commenced, in many countries.
[d] Before global eradication proposed, in several countries.
[e] But since 1985 considerable help provided by UNICEF, the World Bank, and others.

The **most important differentiating feature** between smallpox and other rash illnesses, particularly chicken pox (Herpes Zoster) is the presence in smallpox of fever **before** onset of rash

	SMALLPOX	CHICKENPOX
FEVER	2 to 4 days before rash	At time of rash
RASH		
• ***Appearance***	Pocks at same stage	Pocks in several stages
• ***Development***	Slow	Rapid

In smallpox, fever is present for 2 to 4 days before the rash begins, while with chickenpox, fever and rash develop at the same time.
All the pocks of the smallpox rash are in the same stage of development on any given part of the body and develop slowly. In chickenpox, the rash develops more rapidly, and vesicles, pustules, and scabs may be seen at the same time.



The relative density of rash on different parts of the body should be carefully observed. This diagram illustrates the differences that are usually seen.

In smallpox (shown in the lower photograph), pocks are usually present on the palms of the hands. In chickenpox there may be few or no lesions on the palms of the hands.

Similarly, on the soles of the feet, the smallpox patient may have many lesions but the chickenpox patient will have few or none

Differential diagnosis of smallpox and chickenpox

smallpox

Chickenpox

Differential diagnosis of smallpox and chickenpox

symptoms

Differential Diagnosis

Smallpox
- Severe, febrile prodrome
- 1-4 days before rash
- ≥101ºF
- Other symptoms:
  - prostration
  - headache
  - backache
  - chills
  - abdominal pain
  - vomiting

Varicella
- Mild or no prodrome
- Little or no fever
- No associated symptoms

Lesions

Differential Diagnosis

Smallpox
- Deep, hard lesions
- Round, well circumscribed
- Confluent or umbilicated
- Lesions at same stage of development

Varicella
- Superficial lesions
- Not well circumscribed
- Confluence and umbilication uncommon
- Lesions at all stages of development

Note again the particular points that help to differentiate smallpox from chickenpox:
– in smallpox, the fever precedes the rash by 2 to 4 days,
– the pocks on any part of the body are at the same stage of development, and they develop slowly,
– the pocks are more numerous on the arms and legs than on the body,
– the pocks are usually present on the palms and soles,
– death following smallpox is not uncommon, while in chickenpox death is very rare. When death occurs in a patient in whom chickenpox has been diagnosed, smallpox should always be suspected.

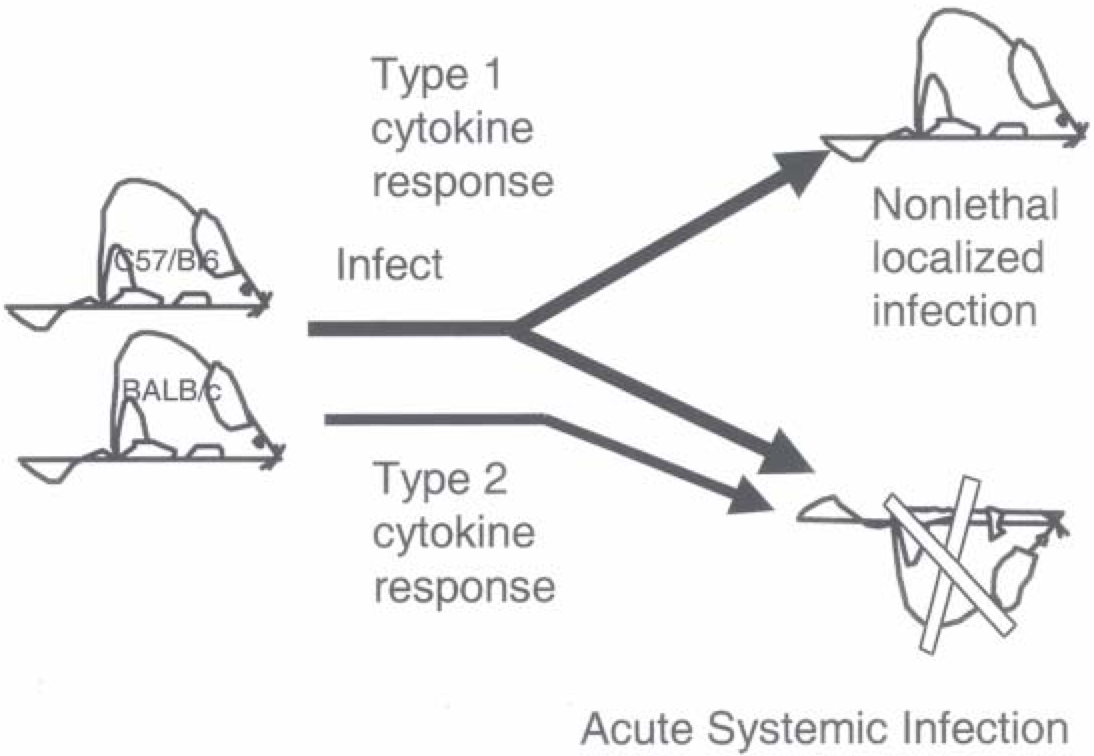
Can smallpox be engineered to overcome vaccination?

- Ectromelia (EV) or mousepox virus is highly lethal in some mouse strains but not others
- EV was engineered to express IL-4
  - the virus became lethal in all mouse strains
  - The virus overcame the protective effects of immunization

Reference: Jackson, R.J.; Ramsay, A.J. et. al., “Expression of mouse interleukin-4 by a recombinant Ectromelia virus suppresses cytolytic lymphocyte responses and overcomes genetic resistance to mousepox. J. Virology (2001) 75: 1205-1210.

Ectromelia (Mousepox) Pathogenesis

Mechanism of smallpox pathogenesis studied primarily using ectromelia, vaccinia and cowpox in inbred mice strains



Increased antiviral effects

↑ **Protective response** (NK, IL-2, IL-12, INF- γ, TNF-α, ↑ ↑ **CTL,** Activated macrophages, NO)

↓ ↓ Virus replication, nonfatal lesions

Increased virulence

↑ Increased non-protective response (IL-4. IL-5. IL-10, IL-13, ↑ Ab)

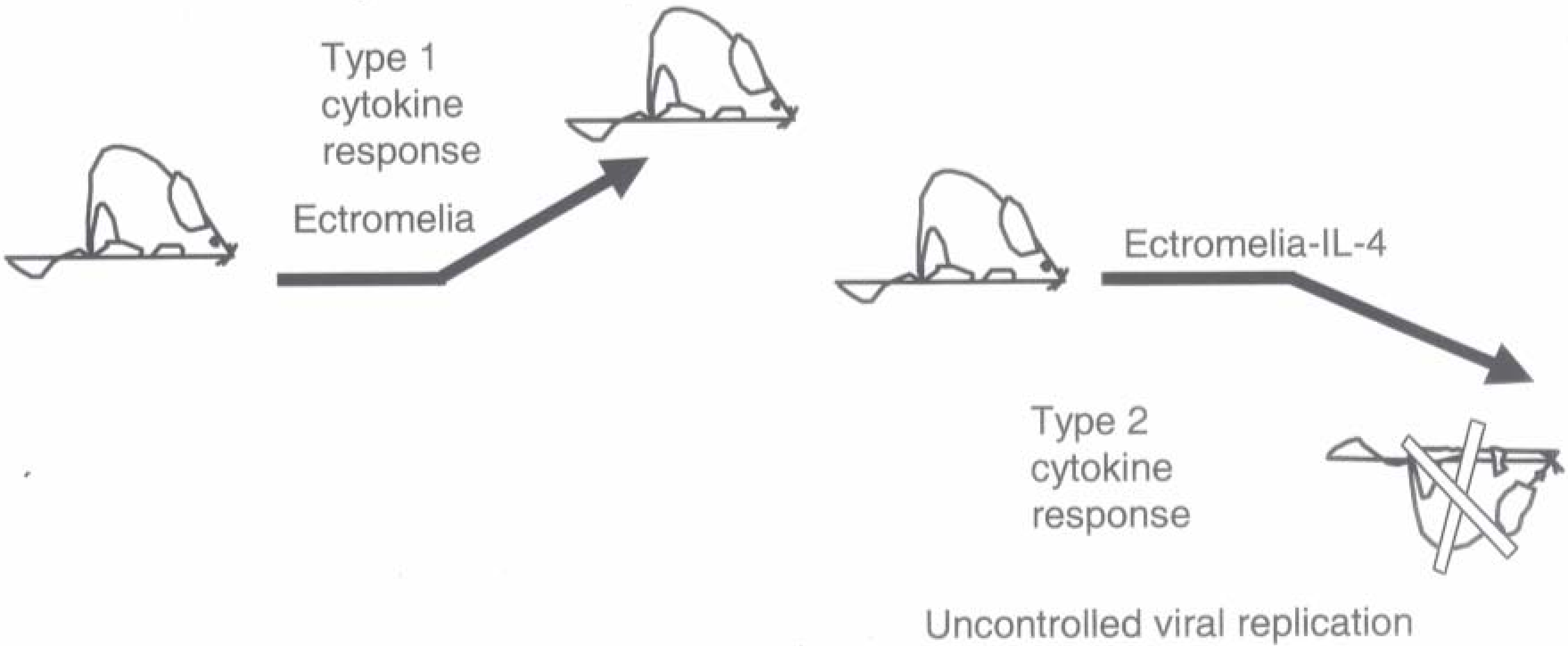
↑ ↑ Virus replication, fatal lesions, ↓ CTL,

Note,, in resistant mice there is an enhanced type 1 cytokine response leading to a robust antiviral host response, IL-4 not involved, the mice survive. However, in strains in which the virus is lethal there is a type 2 cytokine response in which IL-4 is sharply upregulated.

Ectromelia IL-4 recombinants lead to enhance replication and death in normally resistant strains of mice.

Genetically modified orthopoxvirus ectromelia (mousepox) containing an inserted mouse cytokine gene encoding IL-4

- Shifts the immune response from a protective cell-mediated to ineffective antibody- mediated response



Monkeypox an emerging disease

Monkeypox – an indigenous virus of equatorial Africa

- Although not a virus of humans, the clinical symptoms are indistinguishable from smallpox.
- Lethality is only slightly less than smallpox.
- Although not as efficient as smallpox, Human to human transmission has been well documented
- Monkeypox should perhaps be considered a bioterrorist agent

Human Monkeypox (photo: WHO)