Viruses as Bioweapons: Which ones and how to cope with them

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Viral Bioterrorism and Biodefense

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Category A agents of bioterrorism

Agent	Disease
Variola major	Smallpox
Bacillus arthracis	Anthrax
Yersinia pestis	Plague
Clostridium botulinum (toxin)	Botulism
Francisella tularensis	Tularemia
Filoviruses and arenaviruses (e.g. Ebola virus, Lassa virus)	Viral hemorrhagic fever

Rotz *et al*., Emerg. Infect. Dis. 8, 225-230 (2002)

Category B Agents

- Ricin toxin from *Ricinus communis* (castor beans)
- Staphylococcal enterotoxin B
- Typhus fever (*Rickettsia prowazeki*)
- Viral encephalitis [alphaviruses (e.g., Venezuelan equine encephalitis, Eastern equine encephalitis, Western equine encephalitis)]
- Water safety threats (e.g., *Vibrio cholerae*, *Cryptosporidium parvum*)

Category B Agents (continued)

- Brucellosis (*Brucella* species)
- *Clostridium perfringens* toxin
- Food safety threats (e.g., *Salmonella* species, *Escherichia coli*, *Shigella*)
- Glanders (*Burkholderia mallei*)
- Melioidosis (*Burkholderia pseudomallei*)
- Psittacosis (*Chlamydia psittaci*)
- Q fever (*Coxiella burnetii*)

Variola virus is considered as an ideal bioterrorist weapon for the following reasons:

- It is highly transmissible by the aerosol route from infected to susceptible persons.
- The civilian populations of most countries contain a high proportion of susceptible persons.
- Smallpox is associated with high morbidity and about 30% mortality.
- Initially, diagnosis of a disease that has not been seen for 20 years would be difficult.
- At present, other than the vaccine, which may be effective in the first few days post-infection, there is no proven drug treatment available for clinical smallpox.

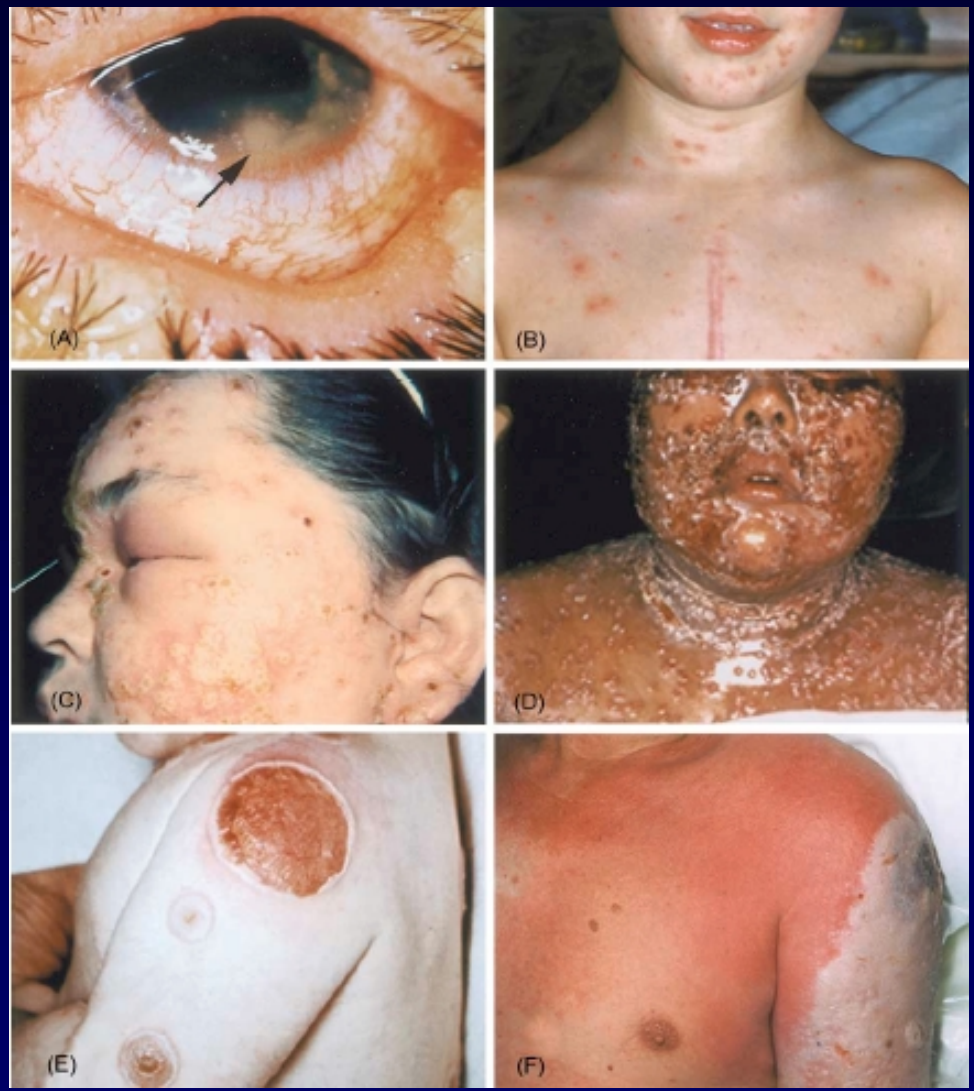
Mahy, Antiviral Res. 57, 1-5 (2003)

Smallpox

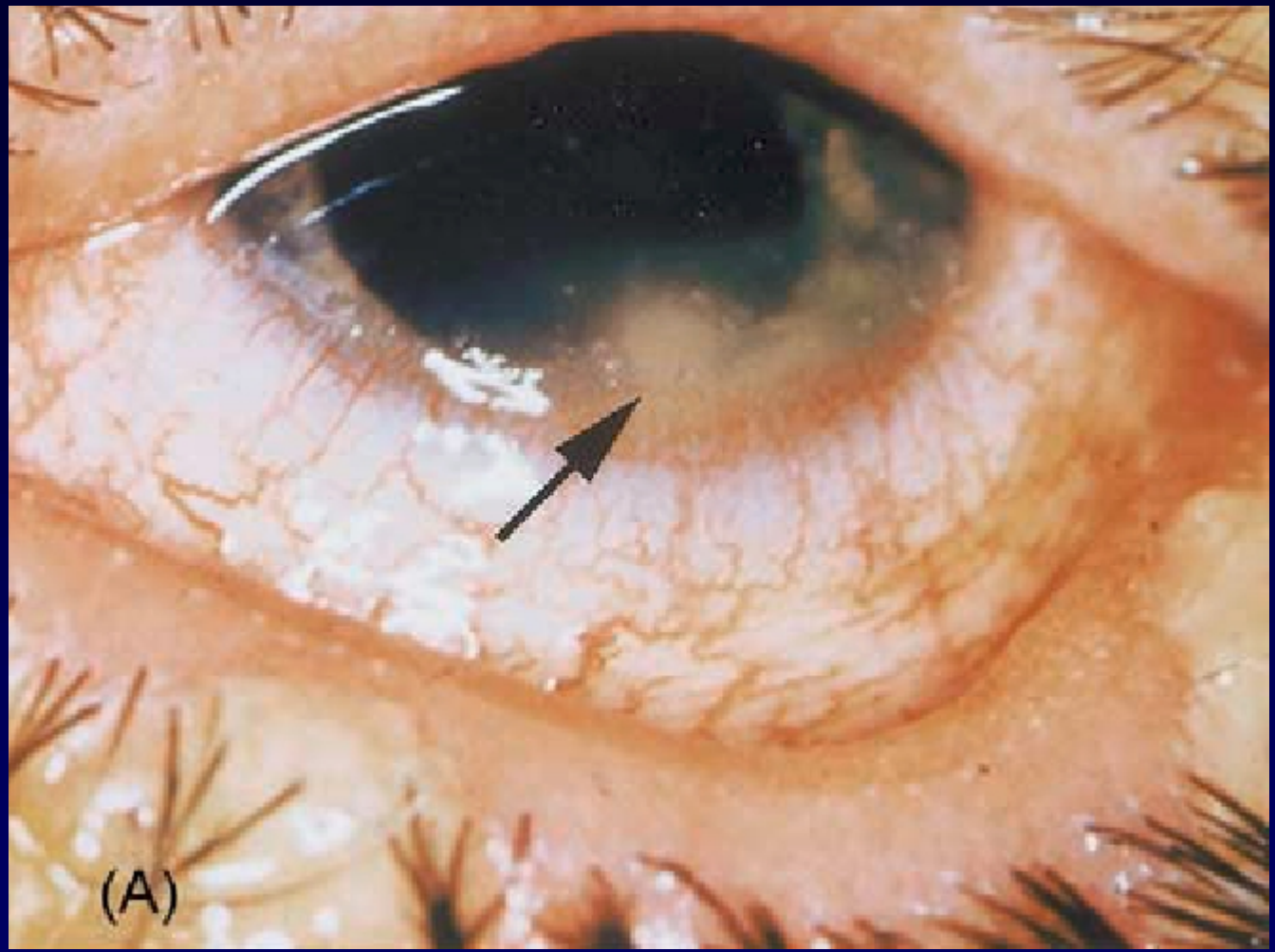
Clinical features	Flu-like symptoms with 2-4 day prodrome of fever and myalgia Rash prominent on face and extremities including palms and soles Rash scabs over in 1-2 weeks
Mode of transmission	Person-to-person
Incubation period	1 day-8 weeks (average 5 days)
Communicability	Contagious at onset of rash and remains infectious until scabs separate (about 3 weeks)
Infection control practices	Contact and airborne precautions
Prevention	Live-virus intradermal vaccine that does not confer lifelong immunity
Postexposure prophylaxis	Smallpox vaccine only within 3 days of exposure
Treatment	There is no licensed antiviral for smallpox (cidofovir is experimental)

Whitley, Antiviral Res. 57, 7-12 (2003)

Complications of vaccination with vaccinia virus

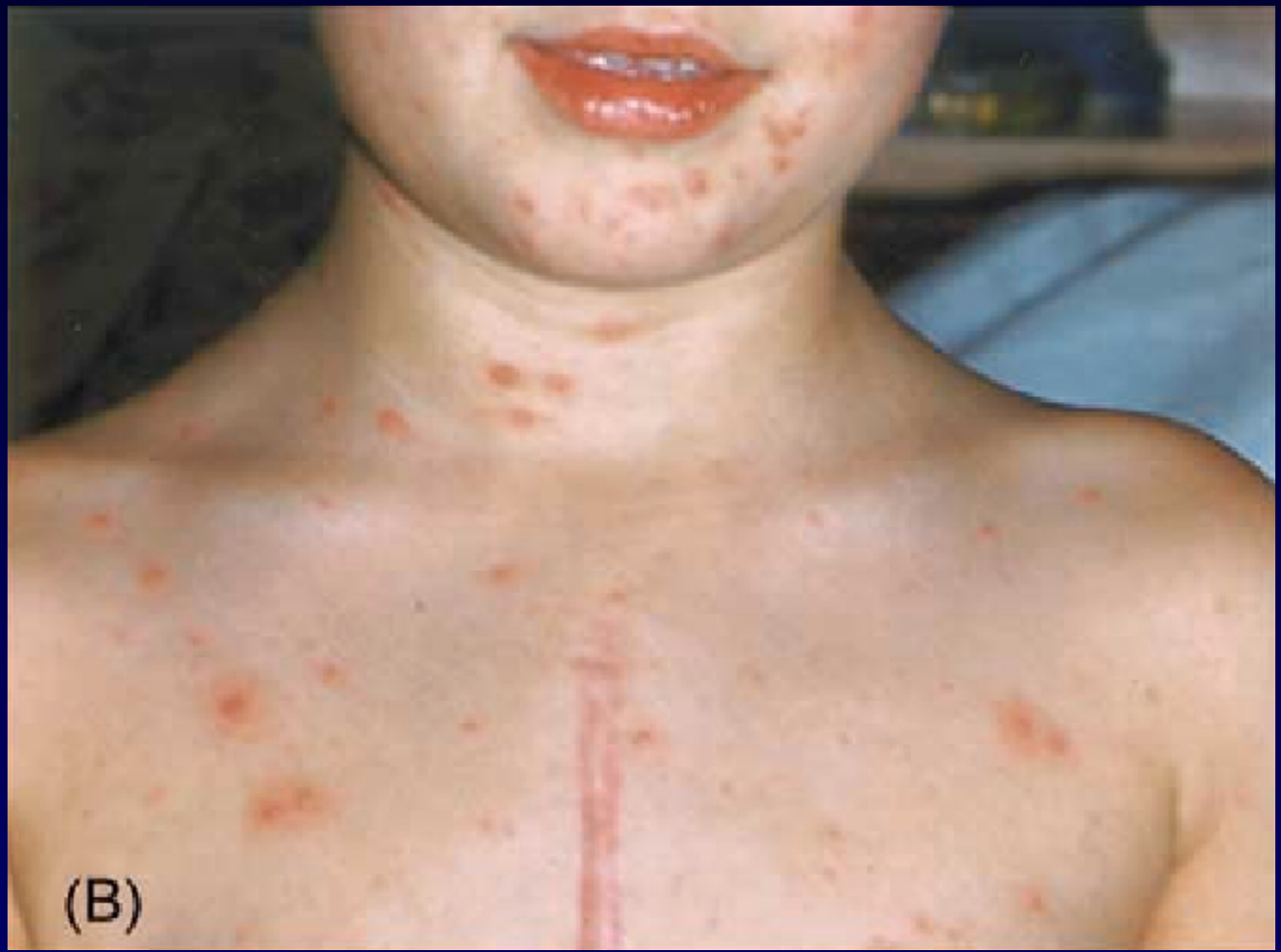


Bray, Antiviral Res., in press (2003)



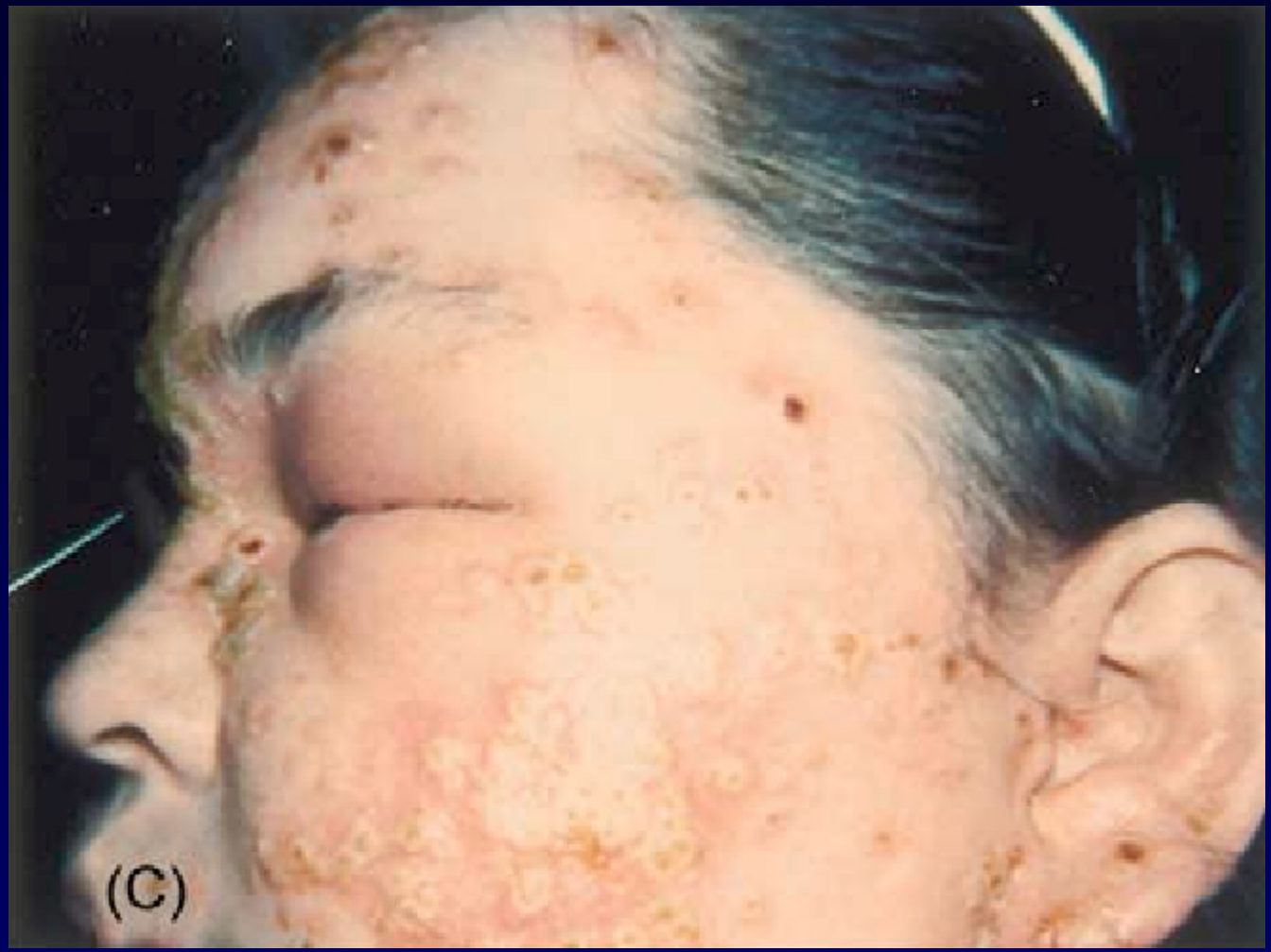
Accidental ocular infection, with conjunctivitis, vascular proliferation and corneal infiltrates (arrow).

Bray, Antiviral Res., in press (2003)



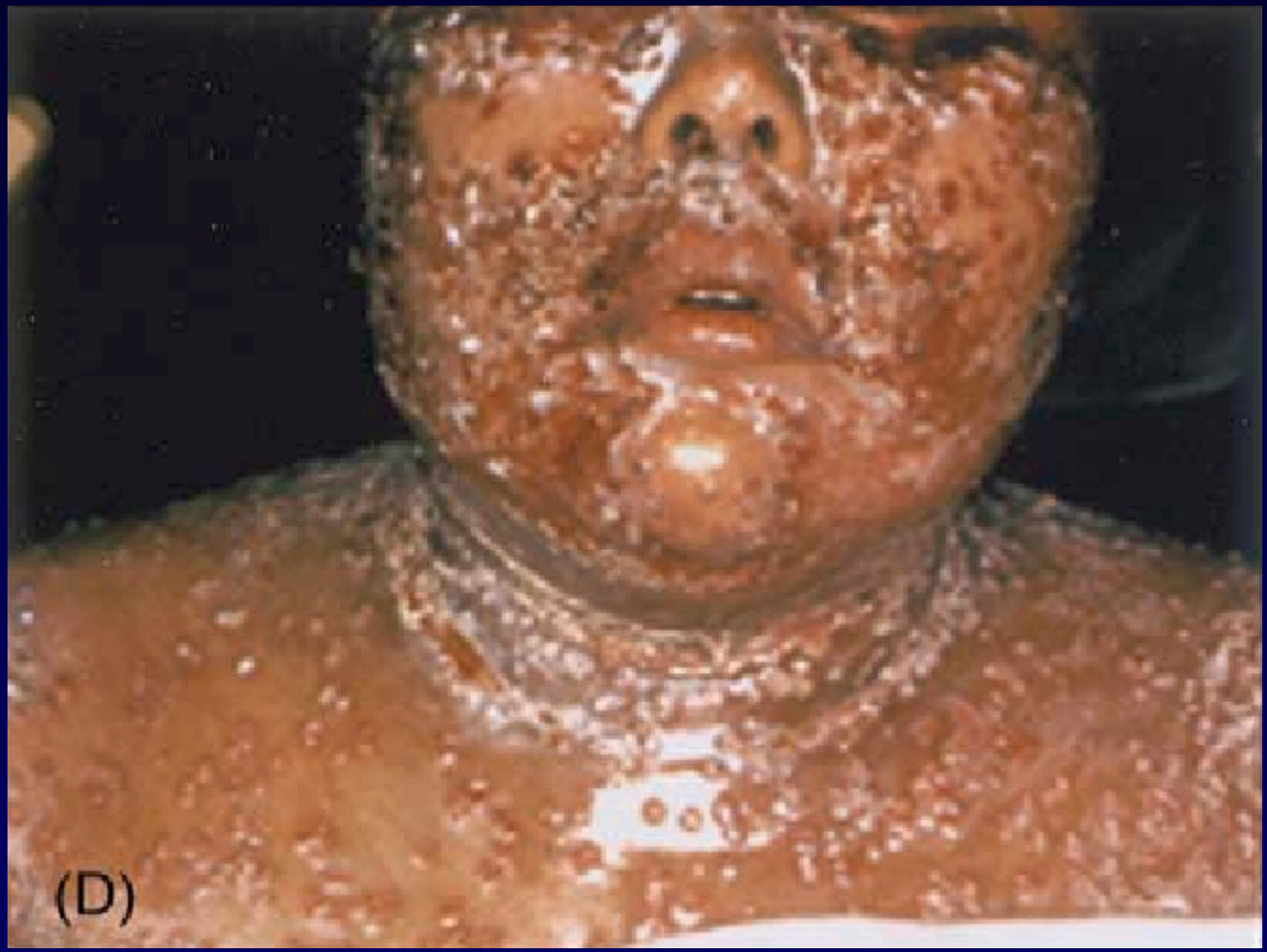
Generalized vaccinia in a primary vaccinee, showing randomly scattered small vaccinia pustules.

Bray, Antiviral Res., in press (2003)



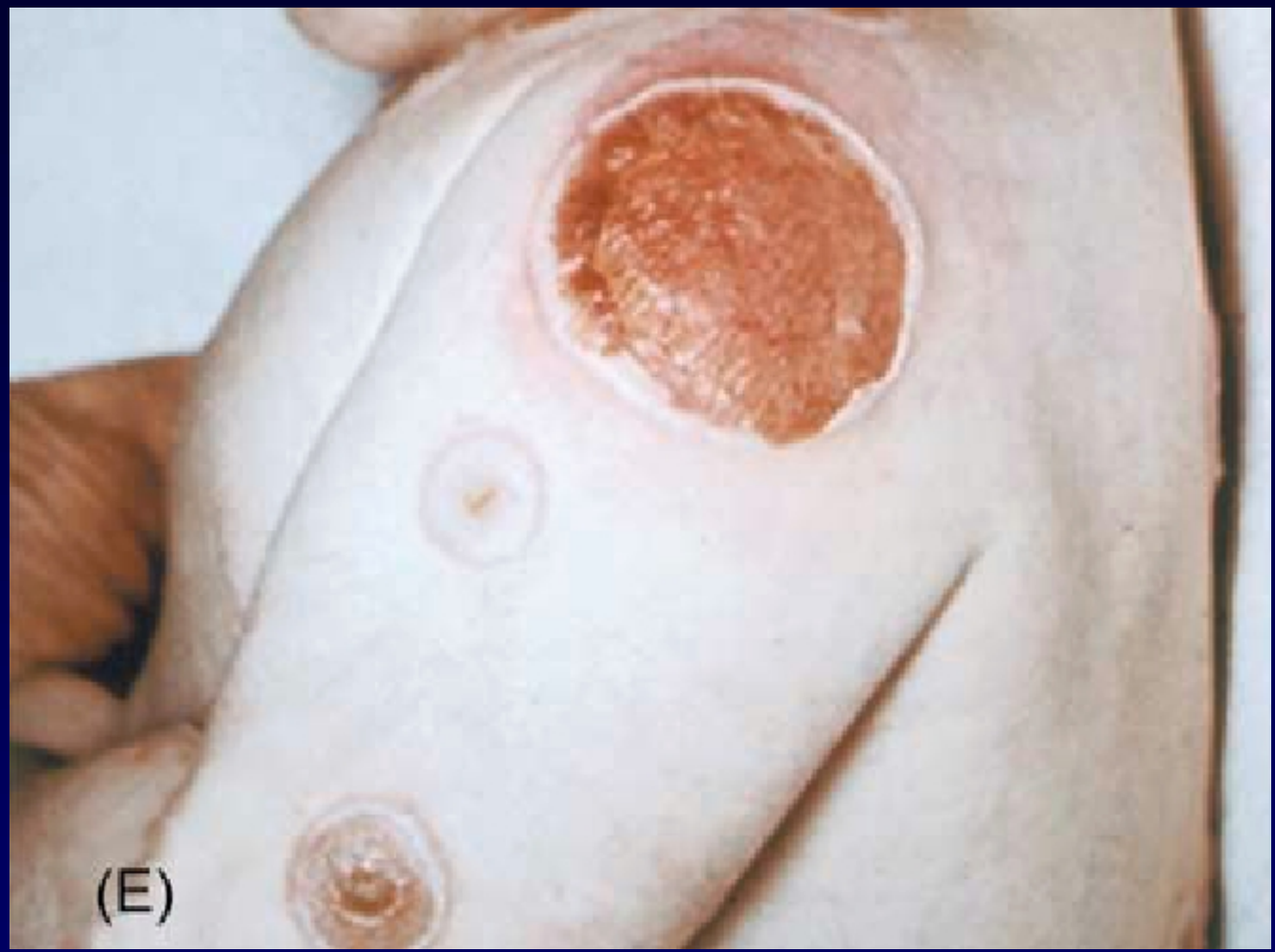
Eczema vaccinatum, showing the development of multiple individual or confluent vaccinia pustules in areas of eczematous skin.

Bray, Antiviral Res., in press (2003)



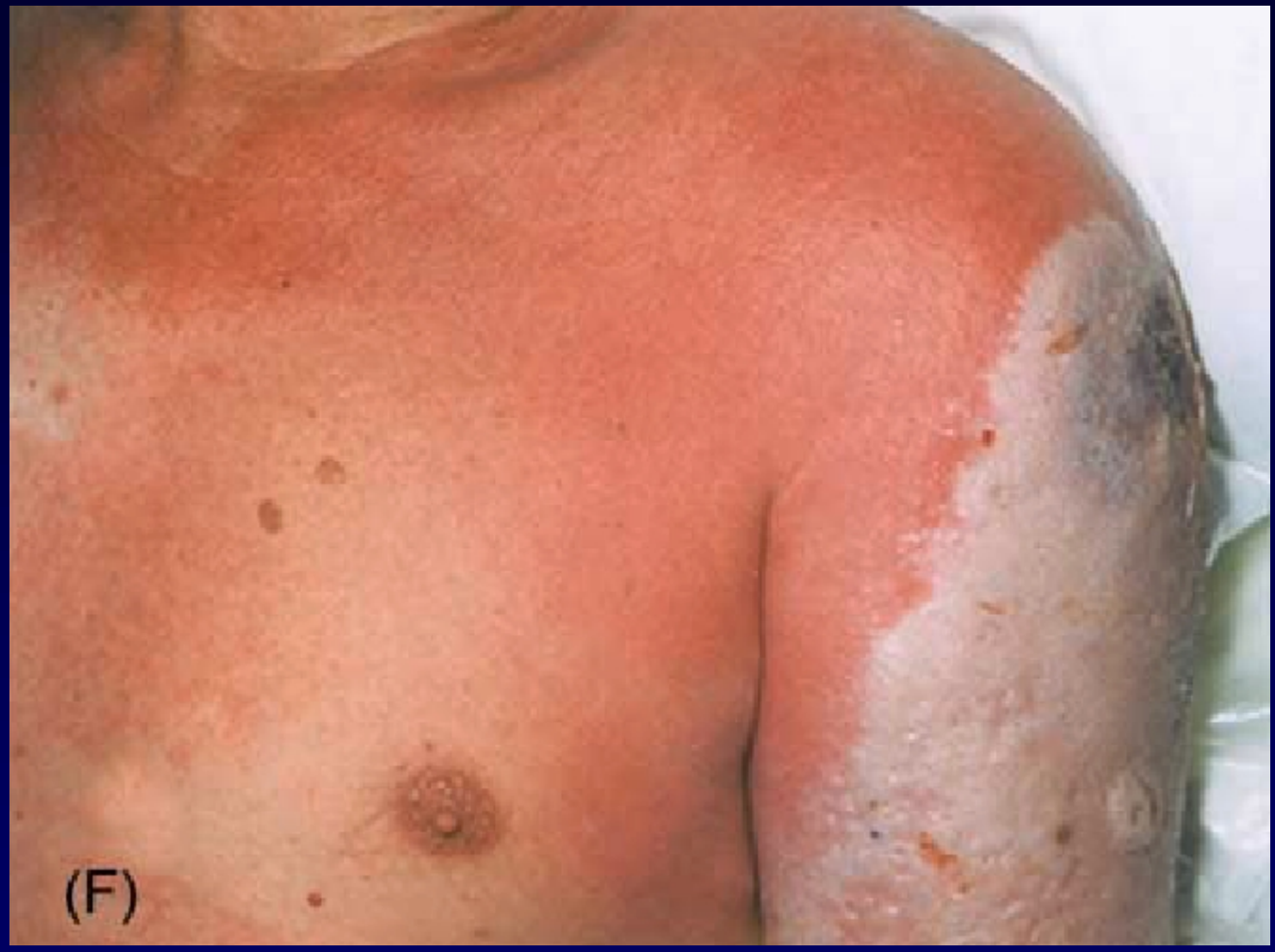
Severe eczema vaccinatum, resembling smallpox, in a 22-year old woman who acquired the infection through contact with her recently vaccinated boyfriend.

Bray, Antiviral Res., in press (2003)



Fatal progressive vaccinia in a 3-month-old infant with severe combined immuno-deficiency. Note absence of inflammation in skin surrounding the lesions.

Bray, Antiviral Res., in press (2003)



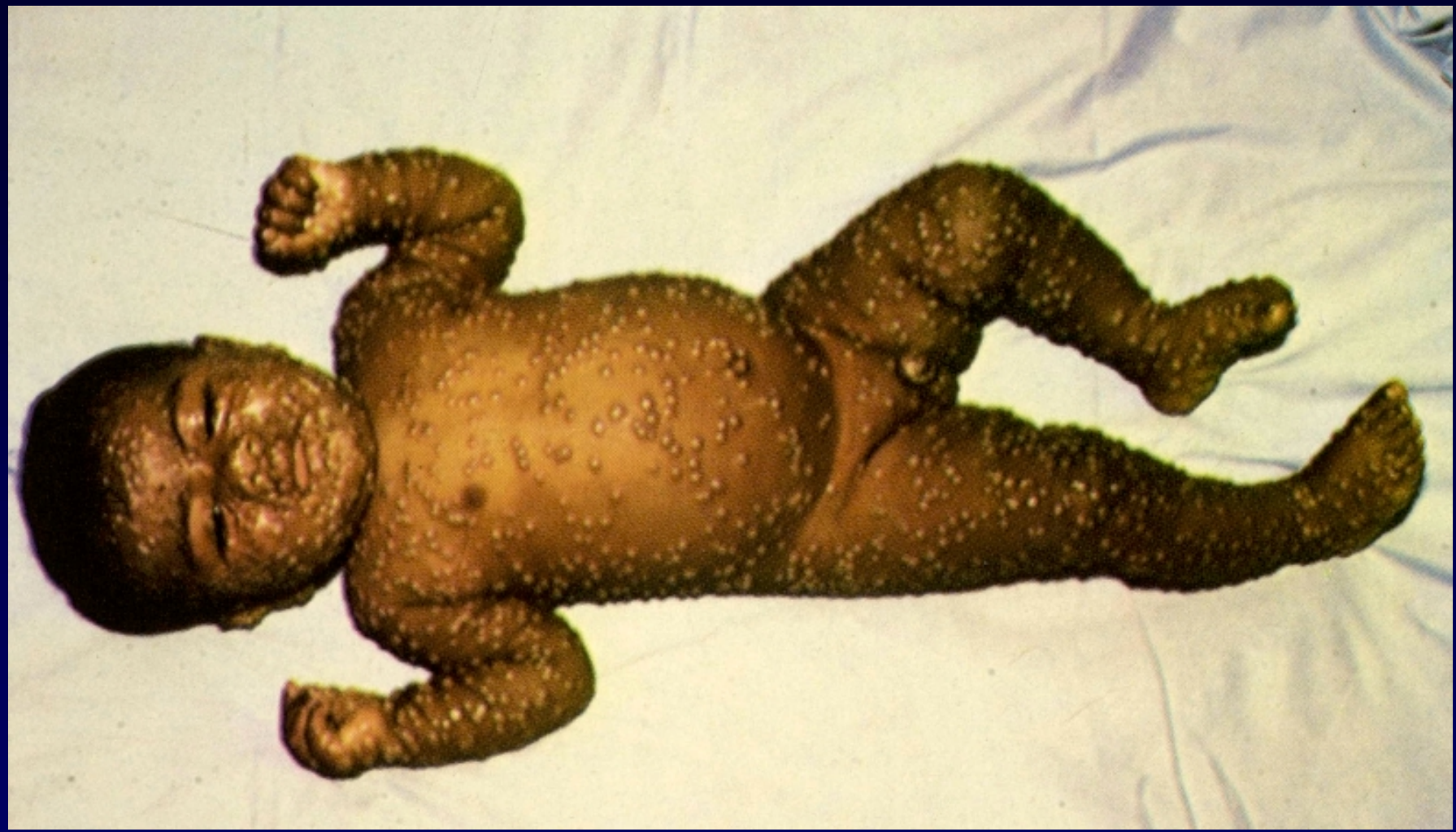
Fatal progressive vaccinia in a 71-year old man with lymphosarcoma. Skin below the necrotic vaccination ulcer contains near-confluent vaccinia vesicles.

Bray, Antiviral Res., in press (2003)

Distribution of smallpox rash – trunk, head and arms.

The centrifugal distribution is pronounced during typical attacks.

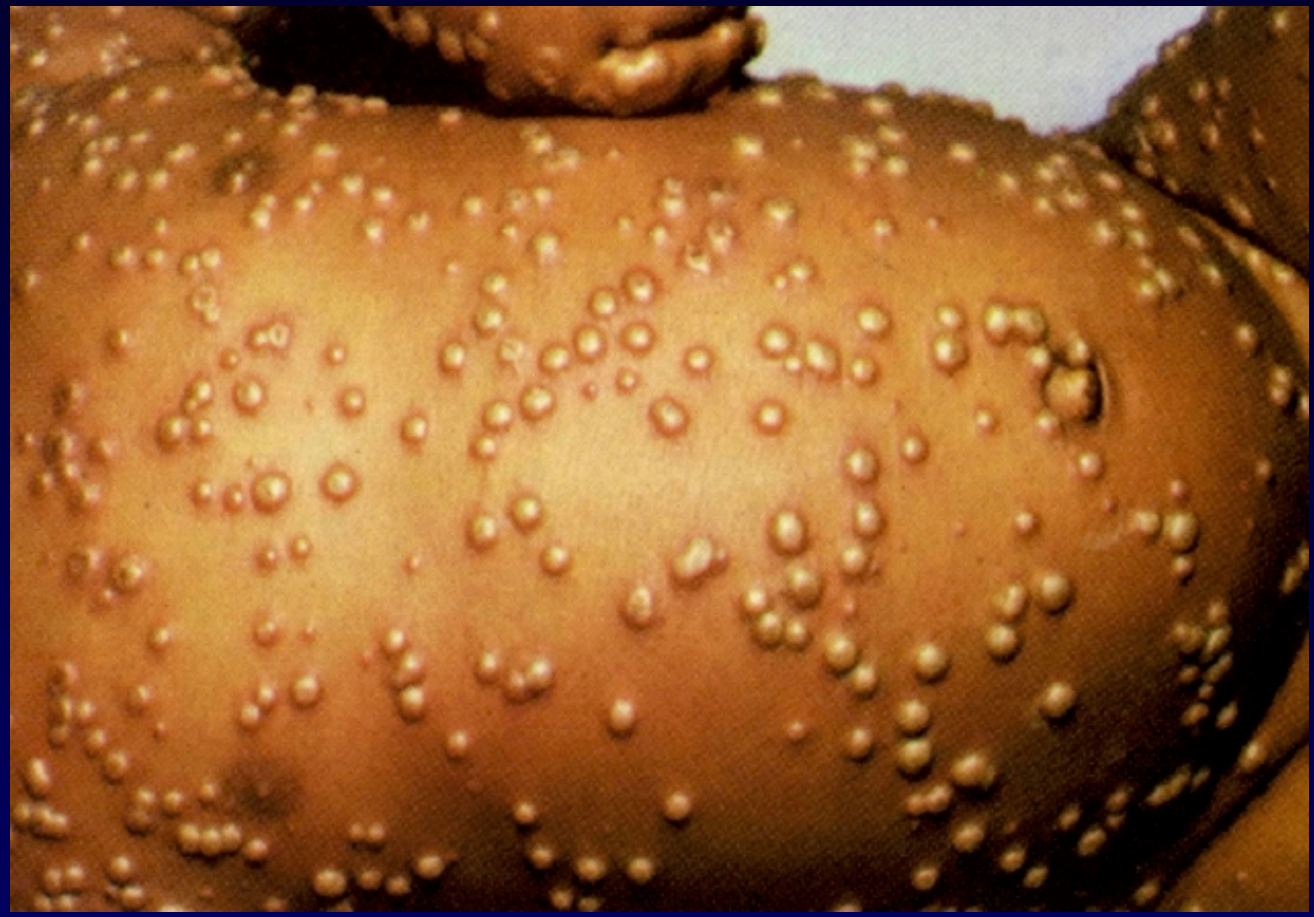
In: A Colour Atlas of Infectious Diseases. R.T.D. Emond, Ed.
Wolfe Medical Books, London (1974)



Distribution of smallpox rash.

The typical rash of smallpox has a centrifugal distribution.

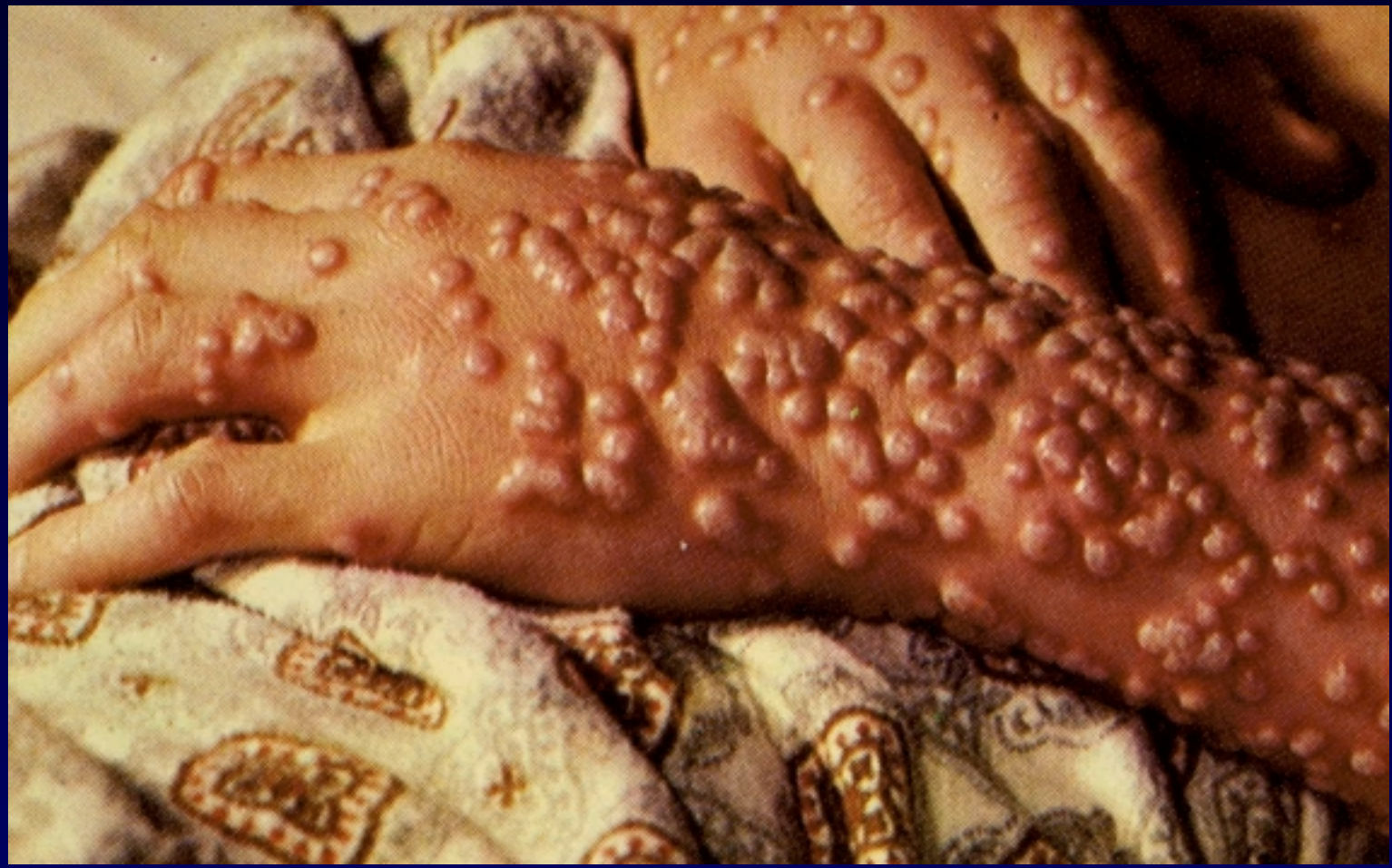
In: A Colour Atlas of Infectious Diseases. R.T.D. Emond, Ed. Wolfe Medical Books, London (1974)



Evolution of smallpox rash – pustules.

By the fifth day of the rash the fluid in the vesicles is beginning to turn cloudy; a further two or three days may elapse before all the vesicles have changed to pustules.

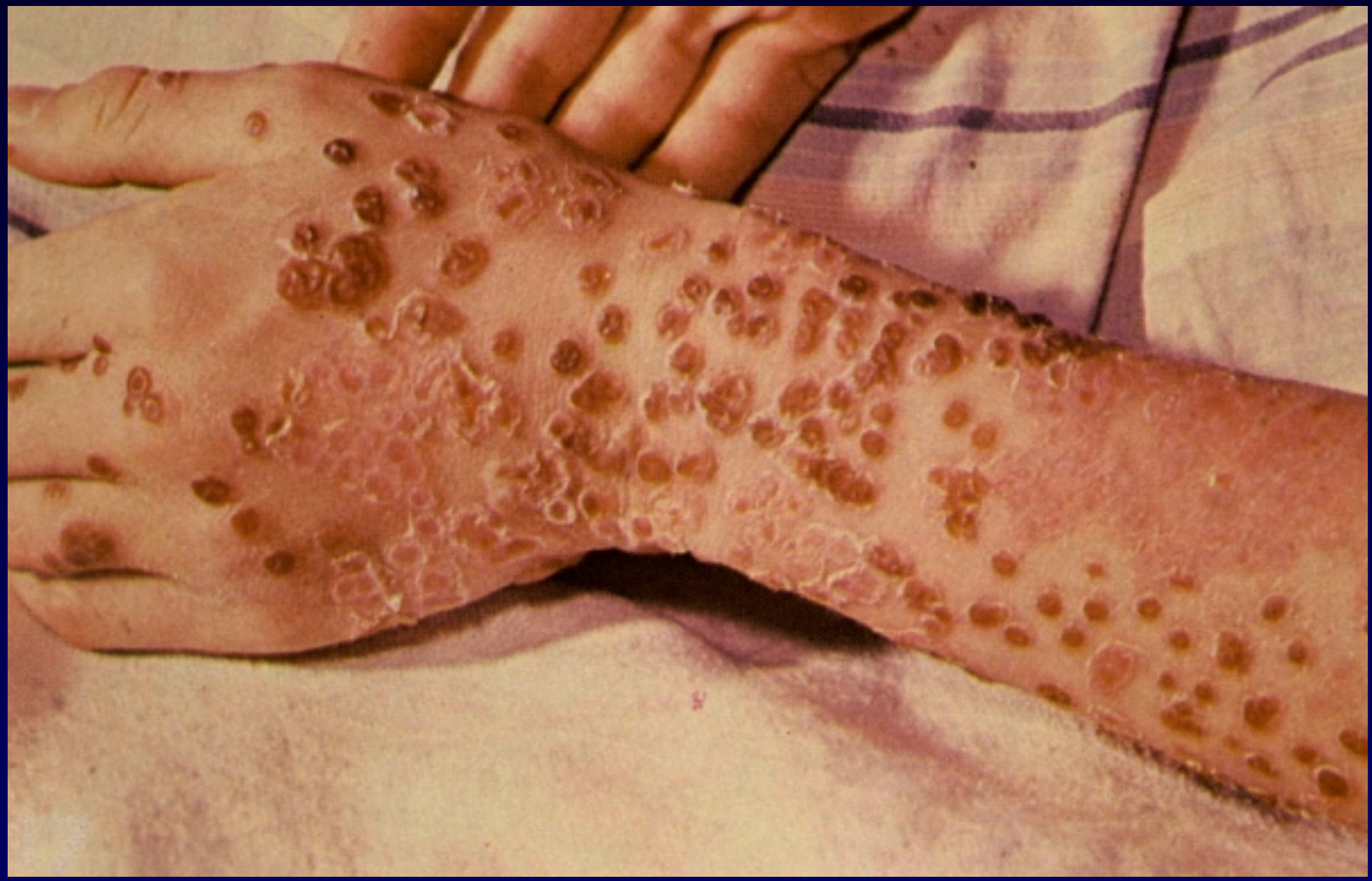
In: A Colour Atlas of Infectious Diseases. R.T.D. Emond, Ed. Wolfe Medical Books, London (1974)



Smallpox – pustules.

Smallpox in the early stages may be mistaken for chickenpox.

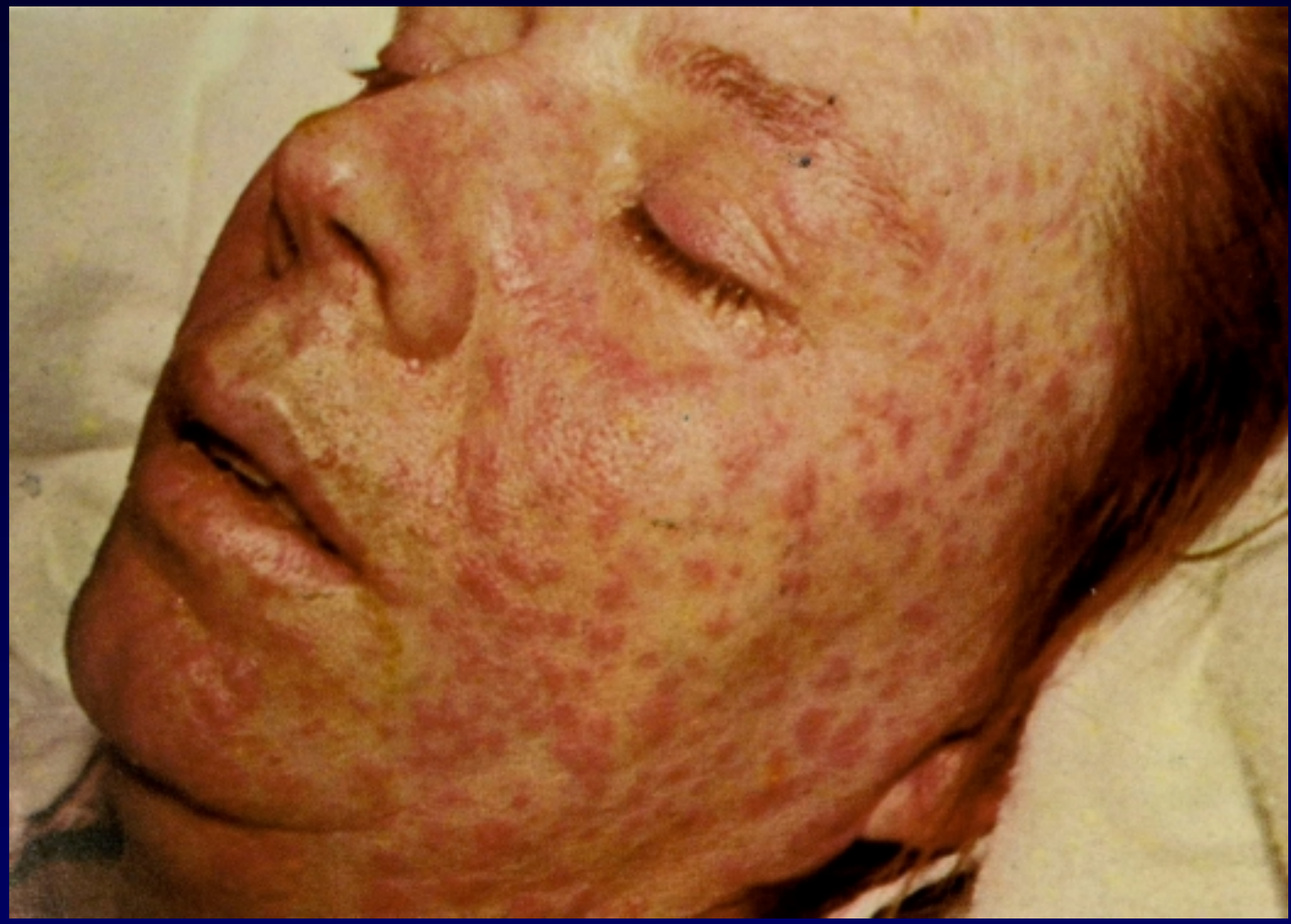
**In: A Colour Atlas of Infectious Diseases. R.T.D. Emond, Ed.
Wolfe Medical Books, London (1974)**



Variola minor – crusts.

The scabs fall off and the skin generally heals without disfigurement.

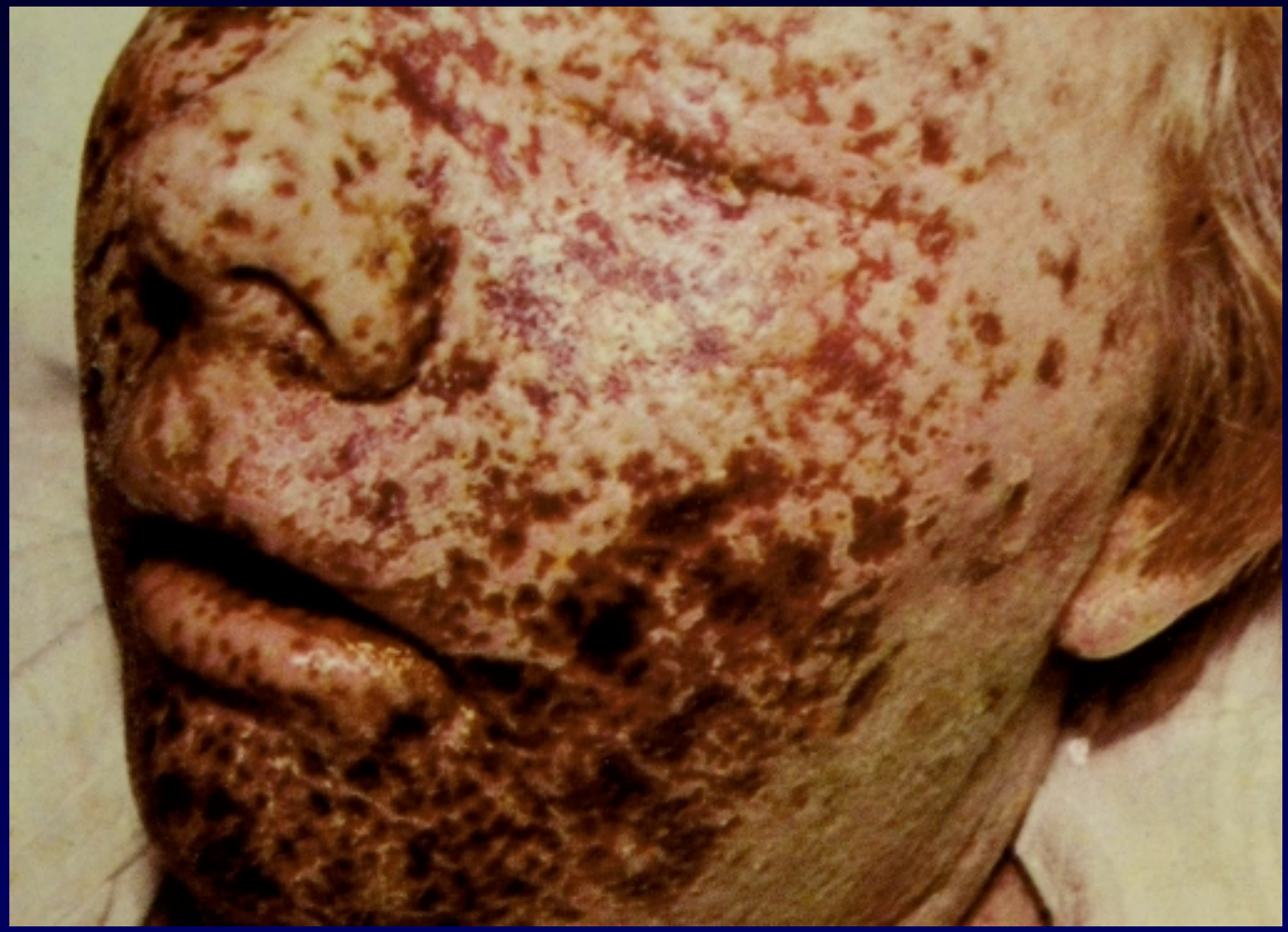
In: A Colour Atlas of Infectious Diseases. R.T.D. Emond, Ed. Wolfe Medical Books, London (1974)



Malignant smallpox – early stage.

Some patients with hypertoxic smallpox die during the prodromal stage before the true rash appears. This patient, a woman of 35 years, is seen on the second day of the focal eruption. The rash is at the papular stage.

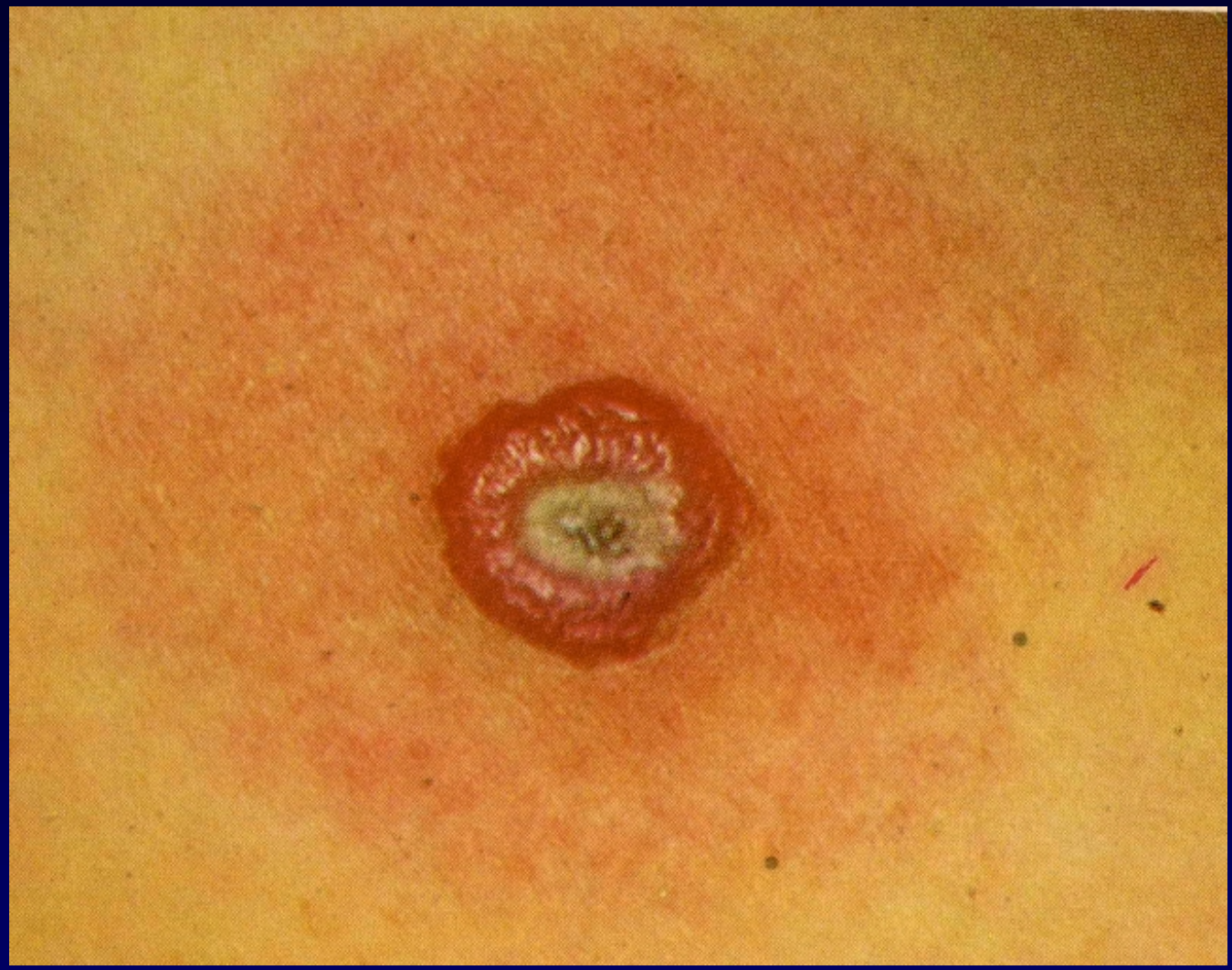
In: A Colour Atlas of Infectious Diseases. R.T.D. Emond, Ed. Wolfe Medical Books, London (1974)



Malignant smallpox – shortly before death.

By the tenth day of the rash there were extensive haemorrhages into the skin of the face but no pustules had developed. The patient died two days later.

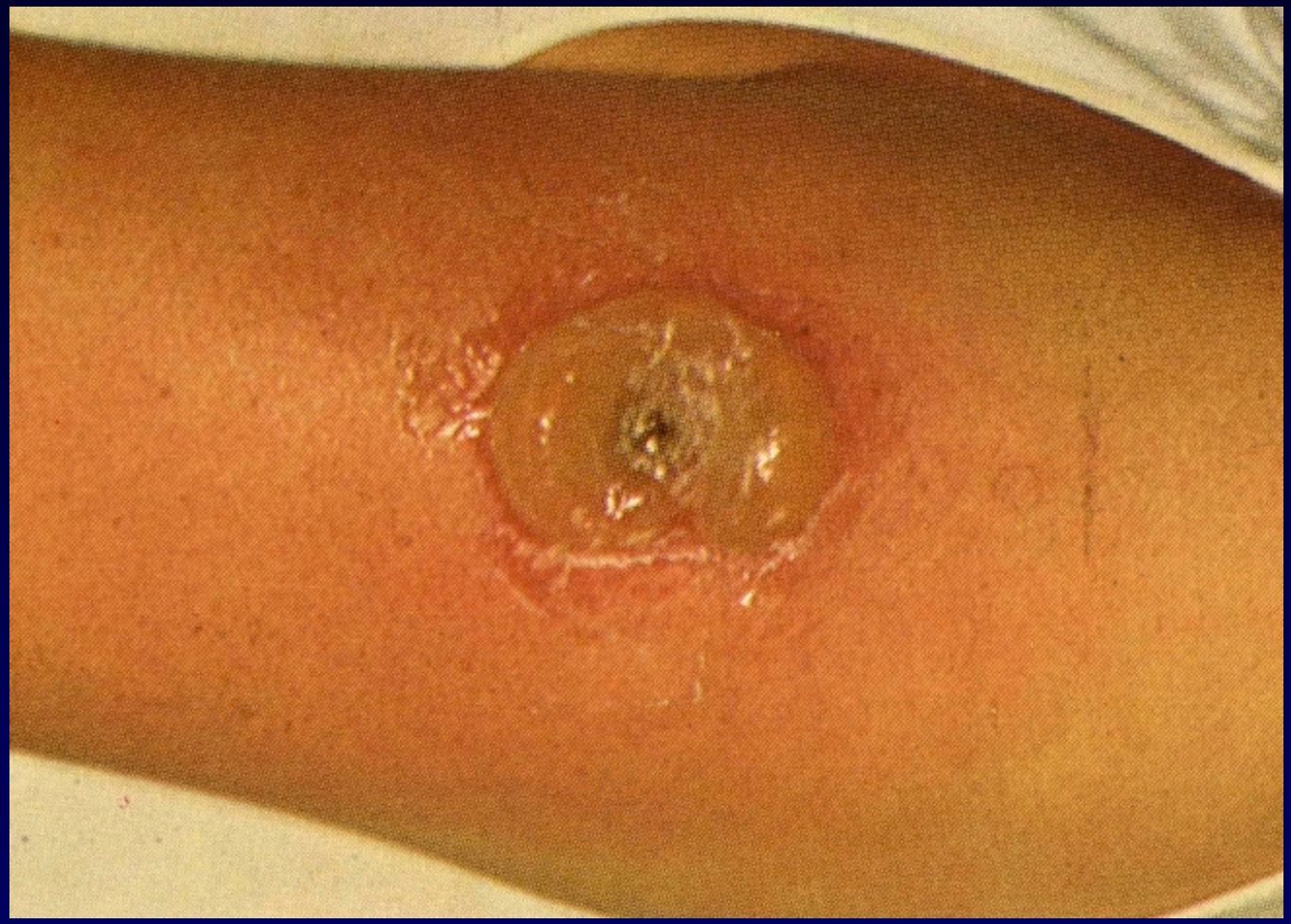
In: A Colour Atlas of Infectious Diseases. R.T.D. Emond, Ed. Wolfe Medical Books, London (1974)



Vaccination – primary reaction.

On the fourth day or so after primary vaccination an itchy papule appears, which becomes vesicular and then pustular.

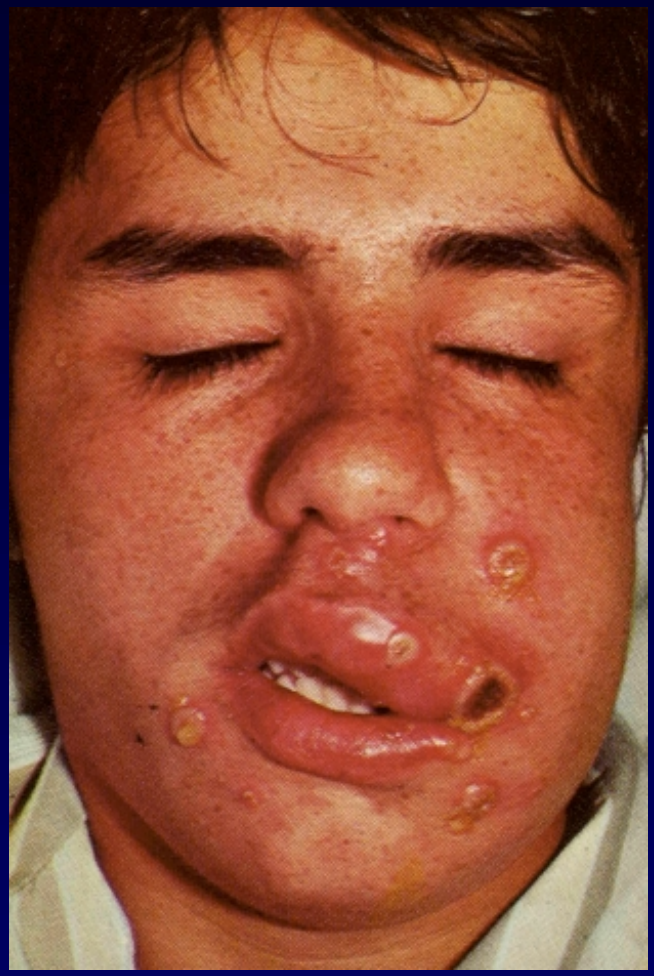
In: A Colour Atlas of Infectious Diseases. R.T.D. Emond, Ed. Wolfe Medical Books, London (1974)



Vaccination – severe primary reaction.

The response to primary vaccination varies with the strain of the virus, the susceptibility of the individual and the technique employed. The illustration shows an exceptionally severe bullous reaction in an unusually sensitive patient.

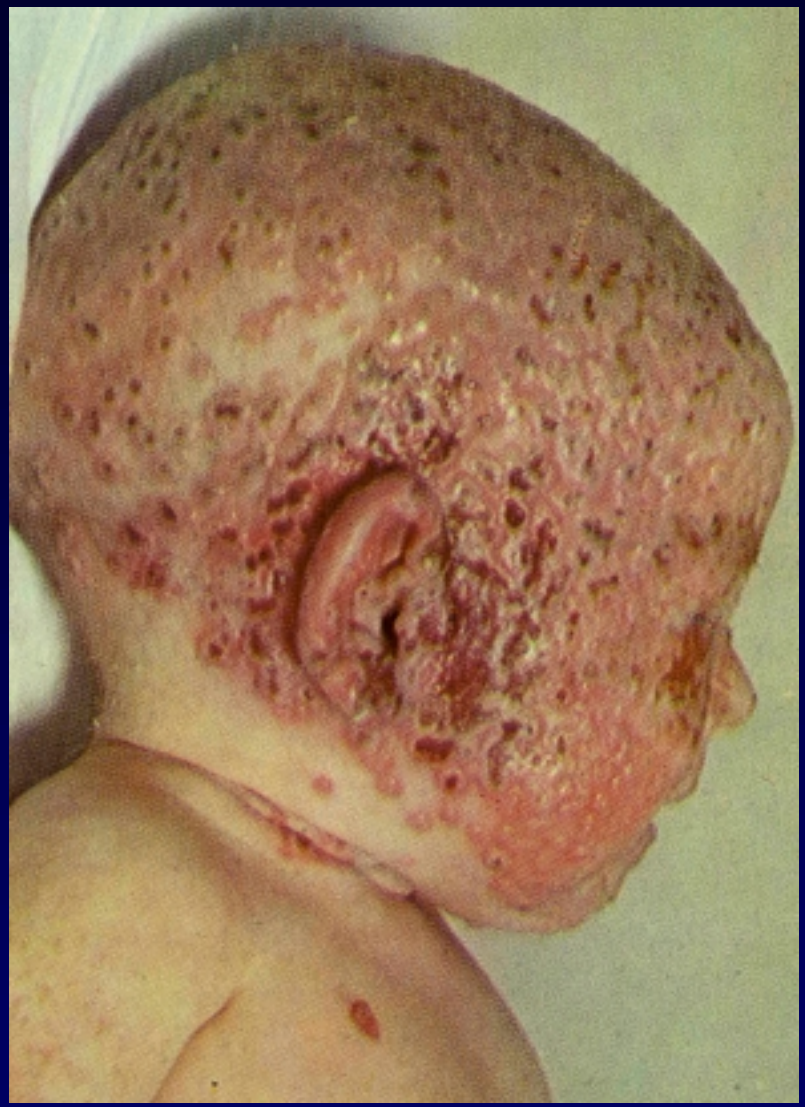
In: A Colour Atlas of Infectious Diseases. R.T.D. Emond, Ed. Wolfe Medical Books, London (1974)



Auto-inoculation following vaccination.

Vaccinia virus may be transferred on fingers, towels or clothing to other parts of the body and inoculated into the skin.

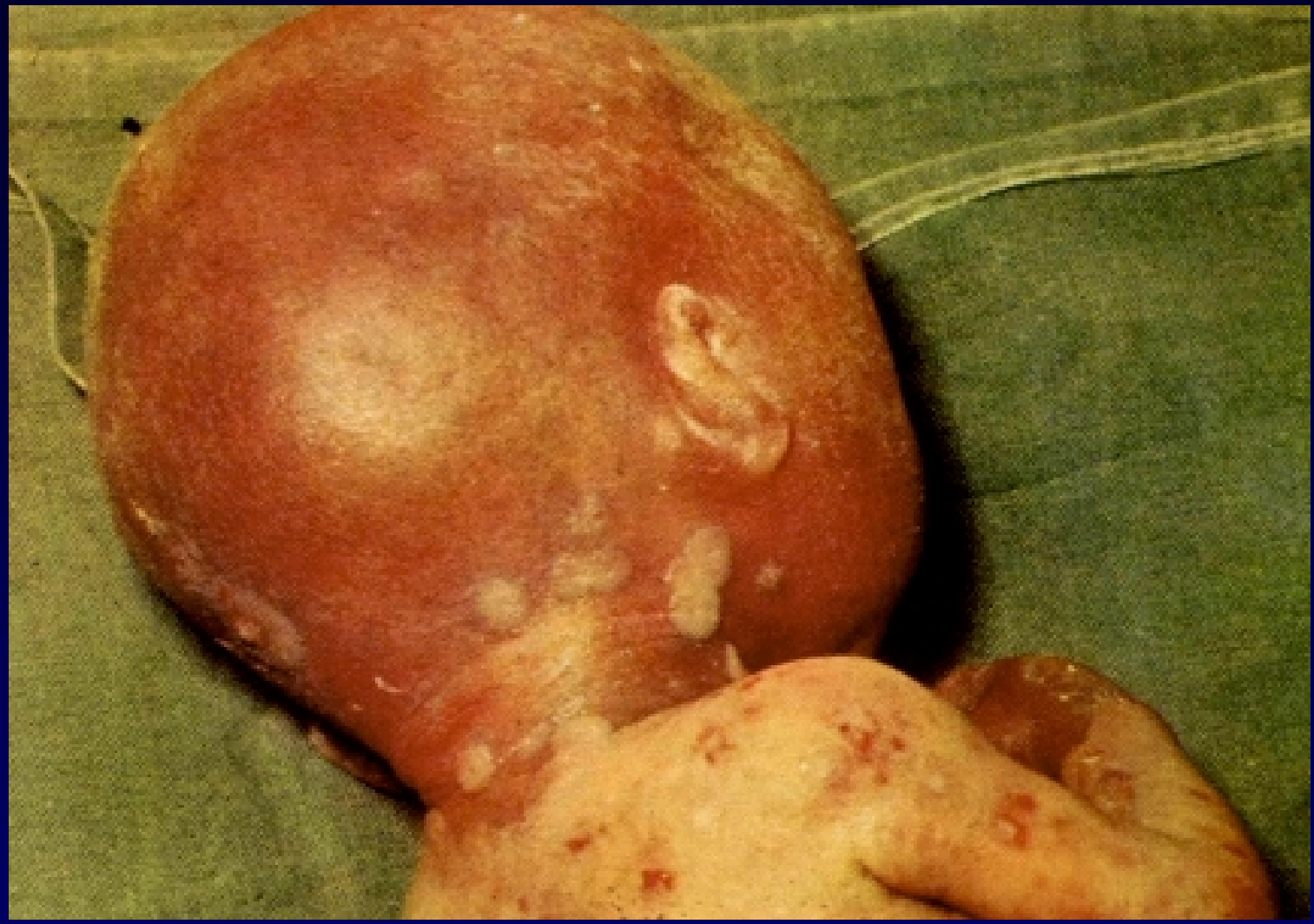
In: A Colour Atlas of Infectious Diseases. R.T.D. Emond, Ed. Wolfe Medical Books, London (1974)



Eczema vaccinatum.

Eczematous patients of all ages are at special risk from vaccinia virus and should not be vaccinated themselves, nor should they be exposed to anyone else who has been recently vaccinated.

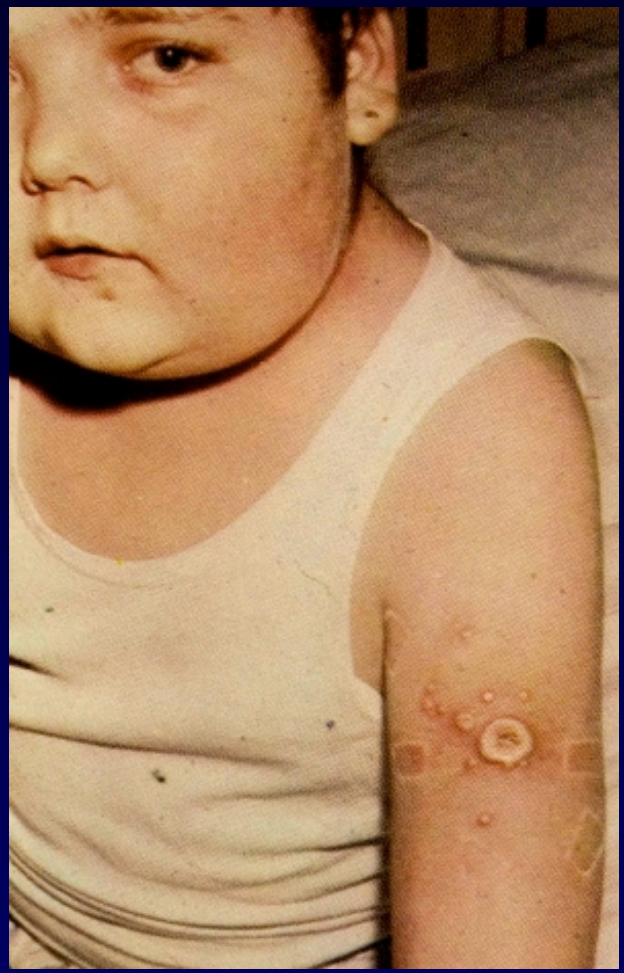
In: A Colour Atlas of Infectious Diseases. R.T.D. Emond, Ed. Wolfe Medical Books, London (1974)



Vaccinia of foetus.

Vaccination is contra-indicated in pregnancy because of the risk to the foetus. The virus is carried in the bloodstream to the placenta and then to the foetus, where it causes generalised infection resulting in death.

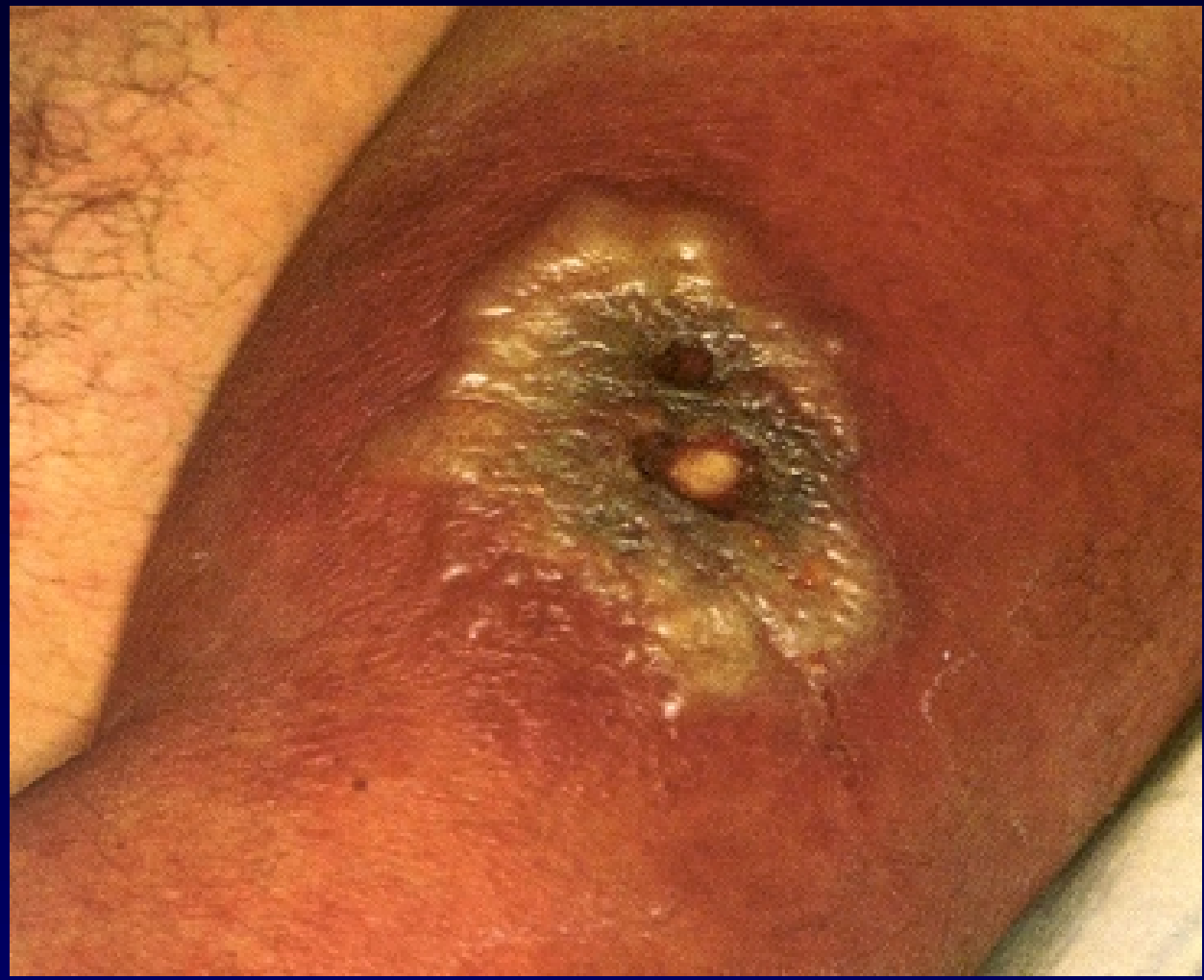
In: A Colour Atlas of Infectious Diseases. R.T.D. Emond, Ed. Wolfe Medical Books, London (1974)



Vaccination and immunosuppressive therapy.

Patients receiving immunosuppressive therapy should not be vaccinated. The child has a typical ‘moon-face’ from corticosteroid therapy and a primary vaccination on his left arm.

In: A Colour Atlas of Infectious Diseases. R.T.D. Emond, Ed. Wolfe Medical Books, London (1974)



Vaccination and disturbed immunity.

Patients with underlying disease, such as carcinomatosis or reticulosis, are especially vulnerable to vaccinia virus and should not be vaccinated. This illustration shows a severe haemorrhagic, gangrenous reaction in a patient with a reticulosis.

In: A Colour Atlas of Infectious Diseases. R.T.D. Emond, Ed. Wolfe Medical Books, London (1974)

Contra-indications for vaccination with smallpox vaccine (vaccinia)

- Immunodeficiency
  - Congenital
  - Acquired (i.e. AIDS)
  - Due to immunosuppressive drugs
    - Cancer chemotherapy
    - Organ transplantation
- Eczema, atopic dermatitis
- Pregnancy
- Infants < 1 year old
- Anyone living in the same house/getting in close contact with any of the above

Physicians will be most likely to suspect a filovirus infection if a previously healthy person becomes abruptly ill with high fever, and shows the following signs and symptoms:

- **hemorrhagic manifestations, perhaps limited to the eyes and mucous membranes;**
- **a maculopapular rash, typically on the trunk, without other skin lesions;**
- **steady worsening of illness to intractable shock, with death within 1 week;**
- **absence of productive cough;**
- **absence of neurologic involvement.**

Bray, Antiviral Res. 57, 53-60 (2003)

Effective defense against filoviruses requires a comprehensive approach that includes the following elements:

- prevention of access to virus stocks;
- improved means of detection of deliberately induced disease outbreaks;
- rapid medical recognition of the viral hemorrhagic fever syndrome;
- rapid laboratory identification of filoviruses in patient specimens;
- prevention of person-to-person transmission;
- reliable decontamination procedures;
- development of effective vaccines;
- development of effective antiviral therapy.

Bray, Antiviral Res. 57, 53-60 (2003)

Viral diseases (VHF) imported into Europe in the recent years

Date	Country of origin	Imported to	Pathogen	No. of cases/ fatalities	Business/tourist
November 1994	Ivory Coast	Switzerland	Ebola virus	1/1	Business
April 1996	Brazil	Switzerland	Yellow fever virus	1/1	Unknown
February 1998	Zimbabwe	UK	CCHF virus	1/1	Unknown
August 1999	Ivory Coast	Germany	Yellow fever virus	1/1	Business
January 2000	Ghana, Ivory Coast, or Burkina Faso	Germany	Lassa virus	1/1	Tourist
February 2000	Sierra Leone	UK	Lassa virus	1/1	Business
March 2000	Nigeria	Germany	Lassa virus	1/1	Nigerian citizen
June 2000	Sierra Leone	The Netherlands	Lassa virus	1/1	Business
March 2001	Chile/Argentina	France	Hantavirus (Andes virus)	1/0	Tourist
May 2001	Kenya	Germany	Dengue virus (hemorrhagic symptoms)	1/0	Tourist
November 2001	The Gambia	Belgium	Yellow fever virus	1/1	Tourist

Drosten *et al*., Antiviral Res. 57, 61-87 (2003)

Arenaviruses

Virus	Distribution	Reservoir	Human significance	Cat. A
Junin	Argentina	*C.musculinus*	Yes	Yes
Machupo	Bolivia	*C.callosus, C.laucha*	Yes	Yes
Guanarito	Venezuela	*Z.brevicauda*	Yes	Yes
Sabia	Brazil	Unknown	Yes	Yes
Lassa	Nigeria, Ivory Coast, Guinea, Sierra Leone	*Mastomys sp.*	Yes	Yes
Lymphocytic choriomeningitis	Worldwide	*M.musculus*	Yes	No
Tacaribe	Trinidad	*Artibeus* spp. (bat)	Yes	No
Whitewater arroyo	Southwestern USA	*Neotoma albigula, N.mexicana*	Yes	No

Charrel & de Lamballerie, Antiviral Res. 57, 89-100 (2003)

Viruses of the Bunyaviridae family considered of bioterrorism importance

Virus	Genus	Geographic distribution	Disease induced
Crimean-Congo hemorrhagic fever	Nairovirus	Africa, Asia, Europe	Crimean-Congo hemorrhagic fever
Rift Valley fever	Phlebovirus	Africa, Middle East, Southern Asia	Rift Valley fever
Sand fly fever	Phlebovirus	Africa, Asia, Europe	Sand fly fever
Dobrova	Hantavirus	Europe	Hemorrhagic fever with renal syndrome
Hantaan	Hantavirus	Asia	Hemorrhagic fever with renal syndrome
Puumala	Hantavirus	Asia, Europe	Hemorrhagic fever with renal syndrome
Seoul	Hantavirus	Asia	Hemorrhagic fever with renal syndrome
Sin Nombre	Hantavirus	North America	Hantavirus pulmonary syndrome

Sidwell & Smee, Antiviral Res. 57, 101-111 (2003)

Nipah virus

Nipah virus, a newly emerging deadly paramyxovirus isolated during a large outbreak of viral encephalitis in Malaysia, has many of the physical attributes to serve as a potential agent of bioterrorism. The outbreak caused widespread panic and fear because of its high mortality and the inability to control the disease initially. There were considerable social disruptions and tremendous economic loss to an important pig-rearing industry. This highly virulent virus, believed to be introduced into pig farms by fruit bats, spread easily among pigs and was transmitted to humans who came into close contact with infected animals. From pigs, the virus has also been transmitted to other animals such as dogs, cats, and horses.

Lam, Antiviral Res. 57, 113-119 (2003)

Nipah virus (continued)

Nipah virus has a number of important attributes that make it a potential agent of bioterrorism. It is an extremely pathogenic organism with a case mortality in humans close to 40%. Besides causing acute infection, it can also give rise to clinical relapse months and years after infection. Other than ribavirin, there are no specific antiviral drugs to combat the virus and no vaccine will be available in the foreseeable future. Diagnostic capability is limited to very few laboratories around the world. Nipah virus can be easily produced in large quantities in cell culture. It should be possible to stabilize it as an aerosol with the capacity for widespread dispersal. Besides infecting humans, the virus can also infect life stock, domestic animals and wildlife, and is likely to cause additional panic to the population. Since the discovery of Nipah virus, only a handful laboratories have access to the virus. However, because of the natural reservoir, it wil not be difficult to isolate the virus from wildlife, making it readily available to any country. It is, therefore, not too far-fetched to think that Nipah virus can be considered a potential agent for bioterrorism.

Lam, Antiviral Res. 57, 113-119 (2003)

Pathogenic hantavirus genotypes

Hantavirus serotype	Main rodent vector (geographical spread)	Human illness (type of spread)
Hantaan (HTN)	*Apodemus agrarius* (striped field mouse) (Asia, Eastern Russia and Southern Europe)	Severe: KHF, EHF, HFRS (rural)
Seoul (SEO)	*Rattus norvegicus* (brown rat) (worldwide)	Intermediate: HFRS (urban and rural)
Puumala (PUU)	*Clethrionomys glareolus* (red bank vole) (Eurasian continent)	Mild: NE (rural)
Dobrova (DOB)	*Apodemus flavicollis* (yellow necked field mouse) (Balkan, Central and Eastern Europe, Middle-East)	Very severe HFRS (rural ?)
Sin nombre virus (SNV)	*Peromyscus maniculatus* (deer mouse) (Canada and USA)	HPS
New York (NYV)	*Peromyscus leucopus* (white-footed mouse) (Canada and Eastern USA)	HPS
Black Creek Canal (BCC)	*Sigmodon hispidus* (hispid cotton rat) (Eastern and Southern USA to Venezuela, Peru)	HPS
Bayou (BAY)	*Oryzomys palustris* (marsh rice rat) (Louisiana)	HPS
Rio Mamoré (RMV)	*Oligoryzomys microtis* (small-eared rice rat) (Bolivia and Peru)	HPS

EHF: Epidemic hemorrhagic fever; HFRS: hemorrhagic fever with renal syndrome; HPS: hantavirus pulmonary syndrome: KHF: Korean hemorrhagic fever; NE: nephropathia epidemica.

Clement, Antiviral Res. 57, 121-127 (2003)

Hantavirus

Hantaviruses (HTVs) are unlikely candidates for biological warfare (BW) applications, since even the American (SNV) (-like) agents are not always lethal or hemorrhagic. As such, HTVs cannot be compared with other VHF viruses, which are all listed in Category A of CDC's list of potential BW agents, whereas HTV ranks only under Category C. HTVs are very difficult to isolate, even with the means available in the most advanced laboratories. A major obstacle for its use in biological warfare is the lack of interhuman transmission, and the limited amount of evidence that artificial, HTV-loaden sprays would be truly infectious for a substantial period of time. Finally, vaccination programs are already being implemented with success in some Far-Eastern countries with inactivated vaccines.

Clement, Antiviral Res. 57, 121-127 (2003)

Congo-Crimean hemorrhagic fever

In fact, another Old World VHF virus, Congo-Crimean hemorrhagic fever (CCHF) virus, seems much better suited for biological warfare (BW) than hantaviruses: it can readily be cultivated, is highly infective (although not documented so far by aerosol), and is easily transmissible between humans, giving rise to local epidemics and even to nosocomial infections, putting the nursing personnel at high risk. In contrast to HTV infections, CCHF viremia continues throughout disease until the appearance of antibodies in blood heralds clinical recovery, coinciding with the disappearance of circulating virus. The CCHF-induced case-fatality rate of about 30% is much higher than that of most other VHF infections, and no CCHF vaccine is at hand, or even in the pipeline.

Clement, Antiviral Res. 57, 121-127 (2003)

Tick-borne encephalitis virus (TBEV)

TBE is one of the most dangerous human infections occurring in Europe and many parts of Asia. The etiological agent Tick-borne encephalitis virus (TBEV), is a member of the virus genus Flavivirus, of the family *Flaviviridae*. TBEV is believed to cause at least 11,000 human cases of encephalitis in Russia and about 3000 cases in the rest of Europe annually. Related viruses within the same group, Louping ill virus (LIV), Langat virus (LGTV) and Powassan virus (POWV), also cause human encephalitis but rarely on an epidemic scale. Three other viruses within the same group, Omsk hemorrhagic fever virus (OHFV), Kyasanur Forest disease virus (KFDV) and Alkhurma virus (ALKV), are closely related to the TBEV complex viruses and tend to cause fatal hemorrhagic fevers rather than encephalitis.

Gritsun *et al*., Antiviral Res. 57, 129-146 (2003)

TBEV (continued)

- Tick-borne flaviruses are pathogenic for humans and some animals. Some strains are more virulent than others but even the most virulent viruses are unlikely to produce high fatality rates. These viruses can infect via the alimentary tract and also when inoculated intranasally into experimental animals. Presumably, concentrated aerosols or high virus concentrations delivered as a powder contaminating food would be infectious.
- TBEV are excreted in the urine and faeces of experimentally infected animals but it is unlikely that this form of virus would provide an efficient route of infection for humans. Perhaps their greatest weakness as biological weapons is the fact that they are normally transmitted to vertebrate hosts via the bite of an infected tick, and the natural habitat of ticks is the forest or moist thick grassy vegetation as found on uplands.
- This means that humans and even most animals would be a dead-end for virus transmission because few humans are exposed to the bite of a tick.
- Another important factor is that these viruses are all antigenically closely related. Therefore, immunity against one strain is likely to produce cross-immunity against the others. Moreover, in endemic regions there is a reasonably high level of immunity among the indigenous viruses.

Gritsun *et al*., Antiviral Res. 57, 129-146 (2003)

TBEV (continued)

One can ask the question whether or not it is feasible to spread the virus by infecting large numbers of ticks with the virus. This would not be a logical approach for the following reasons: (a) very large numbers of infected ticks would be required and, logistically, this would be technically extremely difficult; (b) ticks only feed three times, at very critical stages of their life cycle and it would be extremely difficult to arrange for them to be infected and ready to feed when delivered as weapons; (c) the production of a sufficiently large number of ticks to pose a threat to human or animal populations would also be a difficult technical exercise.

Gritsun *et al*., Antiviral Res. 57, 129-146 (2003)

Influenza virus

- Influenza A virus has been responsible for widespread human epidemics because it is readily transmitted from humans to humans by aerosol.
- Potential of influenza A virus as a bioterrorist weapon: the high virulence of the influenza A virus
- Development of laboratory methods to generate influenza by transfection of DNAs (reverse genetics)
- Antiviral drugs that are directed at functions shared by all influenza viruses constitute the best line of defense against a bioterrorist attack.
- New antiviral drugs need to be developed, few currently available antiviral drugs should be stockpiled

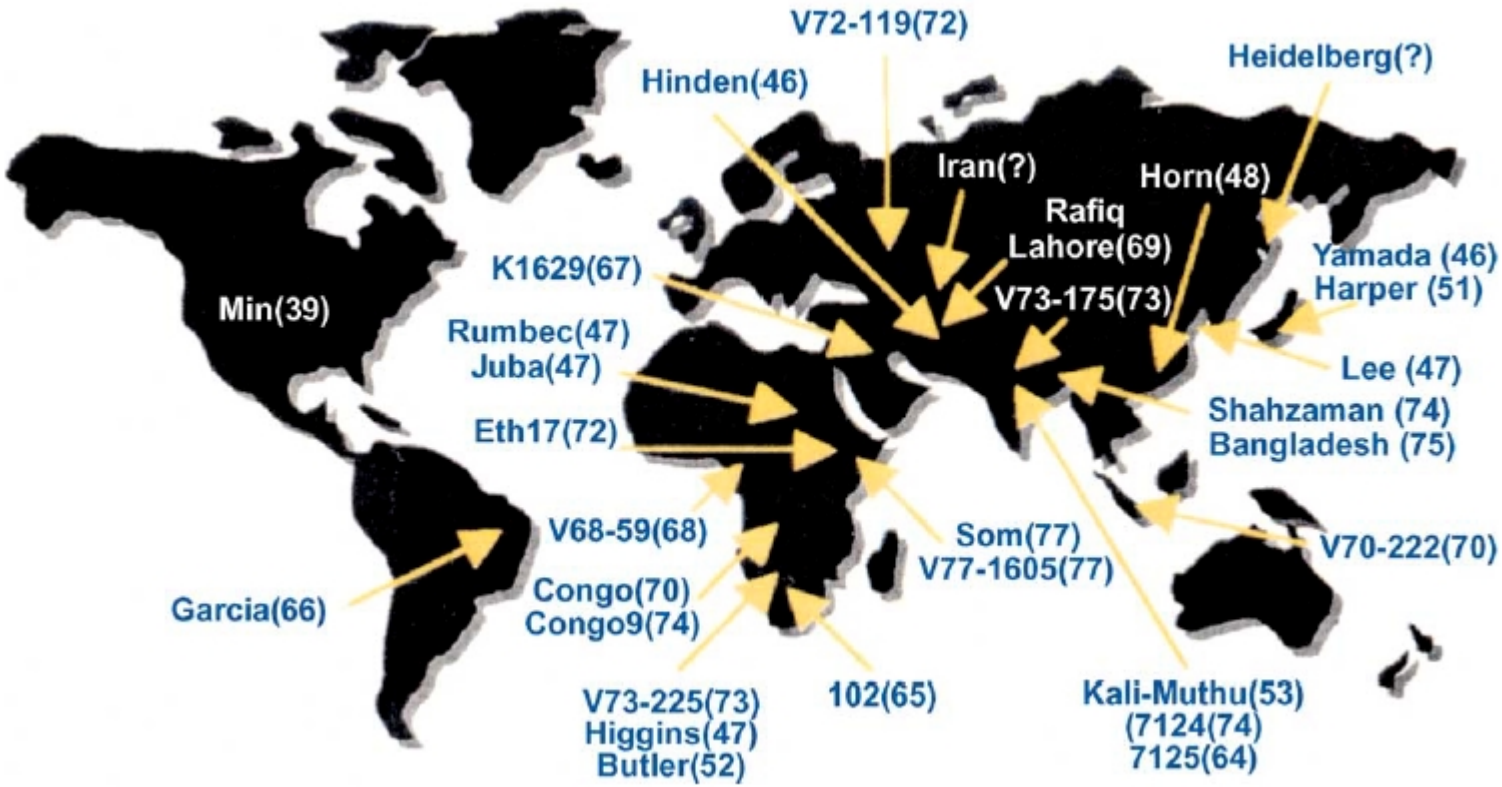
Krug, Antiviral Res. 57, 147-150 (2003)

Influenza virus (continued)

- Lethal human influenza A virus can be generated in the laboratory, utilizing the recently developed reverse genetic system whereby influenza viruses can be generated by transfection of multiple DNAs. Pathogenic H5N1 virus has already been generated using this reverse genetic system.
- It can be argued that most terrorists would not have the knowledge, facilities and ingenuity to carry out these recombinant DNA experiments. This is probably the case at the present time, but the situation can be expected to change in the future, perhaps after as little as 5-10 years.
- Vaccination will probably be of limited value against an influenza virus bioterrorist attack. Currently it takes about 6 months to prepare a vaccine against a new influenza virus strain.
- In addition, the vaccine approach can be readily thwarted by bioterrorists who could spread several influenza viruses with different hemagglutinin (HA) antigenic sites.
- In contrast, antiviral drugs that are directed at functions shared by all influenza A virus strains constitute the best line of defense against a bioterrorist attack. Currently the neuraminidase (NA) inhibitors (zanamivir and oseltamivir) are the only such antivirals available. Consequently, it would be prudent to maintain a stockpile of the NA inhibitors while other antiviral drugs are being developed.

Krug, Antiviral Res. 57, 147-150 (2003)

Variola virus isolate locations and dates



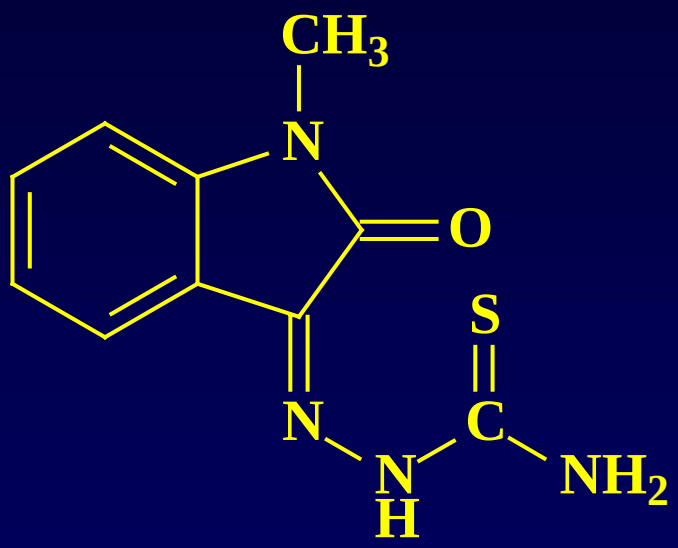
Dates are shown in parentheses and locations of original isolation are indicated by the arrows.

Baker *et al*., Antiviral Res. 57, 13-23 (2003)

IC_{50} values (µg/ml) for cidofovir against all variola virus isolates tested on Vero cells

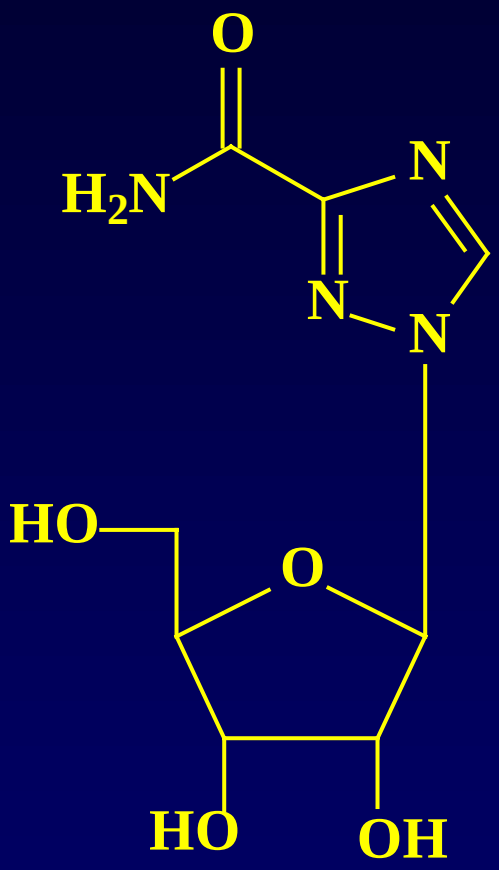
Variola virus isolate	Cidofovir	Variola virus isolate	Cidofovir
Butler	6 ± 4	K1629	17 ± 7
Garcia	7 ± 3	Kali-Muthu	11 ± 0
Minn124	5 ± 1	Jee	10 ± 6
V68-59	13 ± 3	Rafig Lahore	12 ± 9
102	23 ± 6	Rumbec	10 ± 2
7124	20 ± 7	Shahzaman	11 ± 1
7125	12 ± 3	Somalia	7 ± 2
Bangladesh	17 ± 4	V70-46	7 ± 3
Eth17	11 ± 8	V70-222	12 ± 5
Harper	28 ± 13	V72-119	10 ± 5
Heidelberg	15 ± 6	V73-175	12 ± 2
Higgins	14 ± 6	V73-225	5 ± 2
Hinden	10 ± 3	V74-227	10 ± 2
Horn	11 ± 5	V77-1605	19 ± 2
Iran 2602	8 ± 2	Yamada	13 ± 9
Juba	14 ± 3	VAR mean	12 ± 1

Baker *et al.*, Antiviral Res. 57, 13-23 (2003)

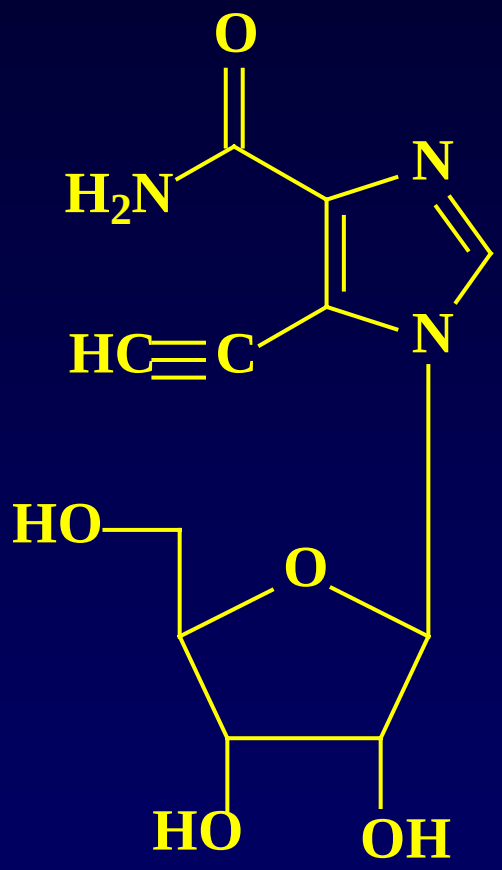


N-methylisatin 3-thiosemicarbazone

IMP dehydrogenase inhibitors

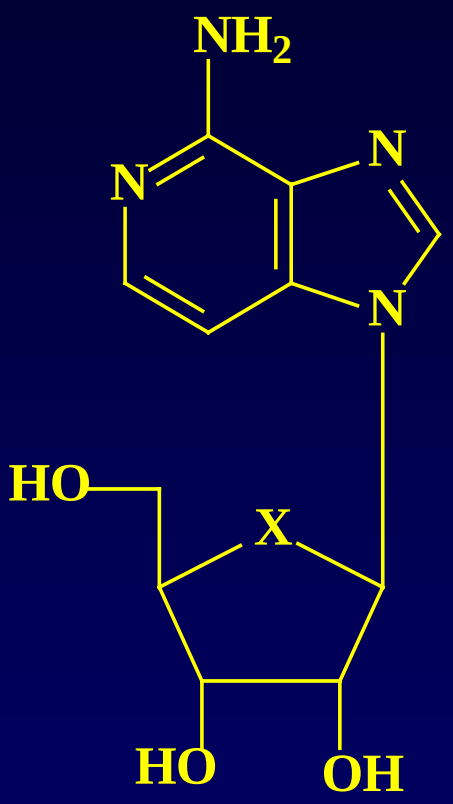


Ribavirin

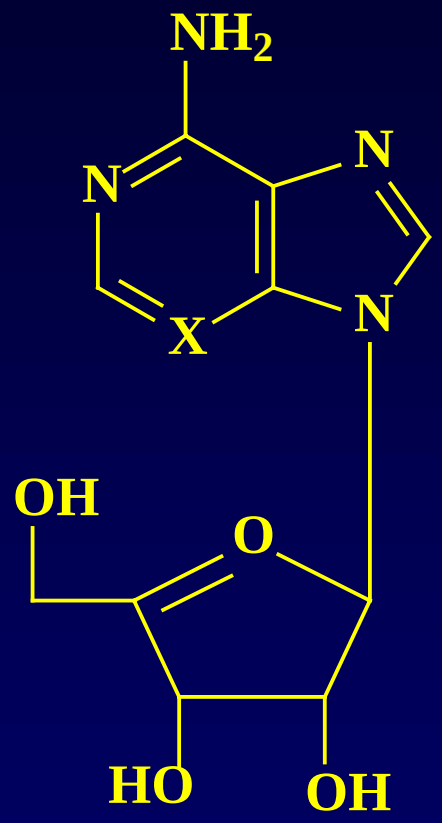


EICAR

SAH hydrolase inhibitors

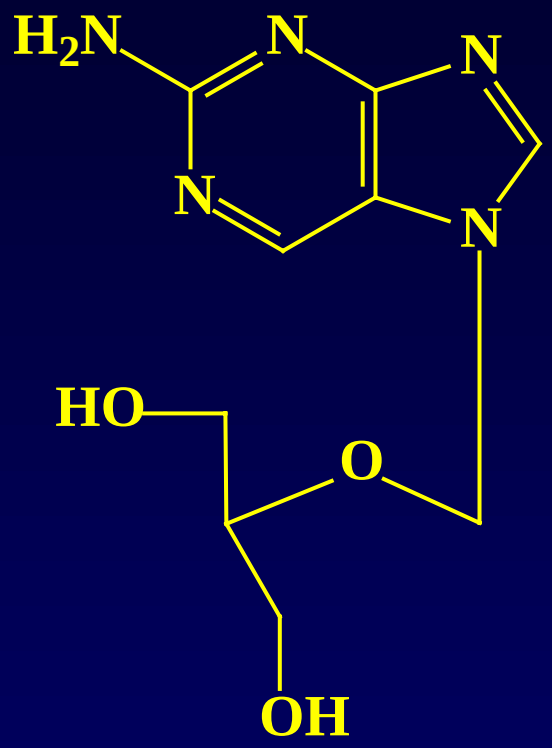


Carbocyclic 3-deazaadenosine
(C-c^{3}Ado)
(X = CH_2)

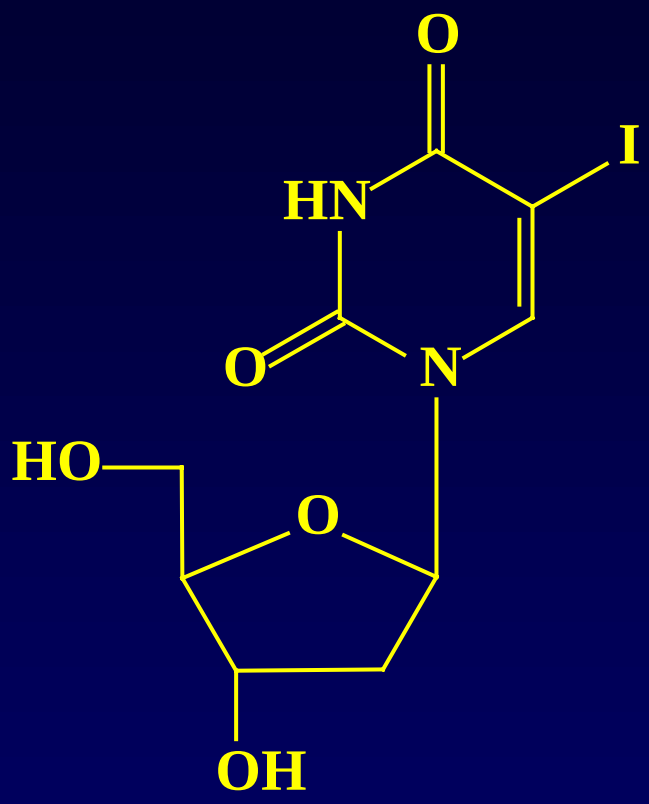


3-Deazaneplanocin A

(X = CH)



S2242



IDU

Cidofovir
(HPMPC)

HDP-HPMPC
HDP-Cidofovir
HDP-CDV

Activity of cidofovir (CDV) and HDP-CDV against vaccinia, cowpox, monkeypox and variola viruses

Compound	EC_{50} (μM)			
	Vaccinia	Cowpox	Monkeypox	Variola
CDV	46.2 ± 11.9	44.7 ± 6.3	4.6	27.3
HDP-CDV	0.8 ± 0.4	0.6 ± 0.3	0.07	0.1

Kern, Antiviral Res. 57, 35-40 (2003)

Efficacy and cytotoxicity of acyclic nucleoside phosphonates against vaccinia virus in HFF cells

Compound	Vaccinia virus EC_{50} (μM)	Cytotoxicity CC_{50} (μM)
HPMPC (CDV)	33 ± 9.1	278 ± 9.2
HPMPA	3.5 ± 2.8	269 ± 21
PMEA	> 366 ± 0	> 366 ± 0
Bis(pivaloyloxymethyl)PMEA	5.1 ± 0.7	117 ± 27
PMEDAP	204 ± 15	> 339 ± 12
PMPA	> 300	> 300
Bis(isopropoxycarbonyloxymethyl)PMPA	> 157	> 157
PMEG	4.0 ± 0.7	88

Kern, Antiviral Res. 57, 35-40 (2003)

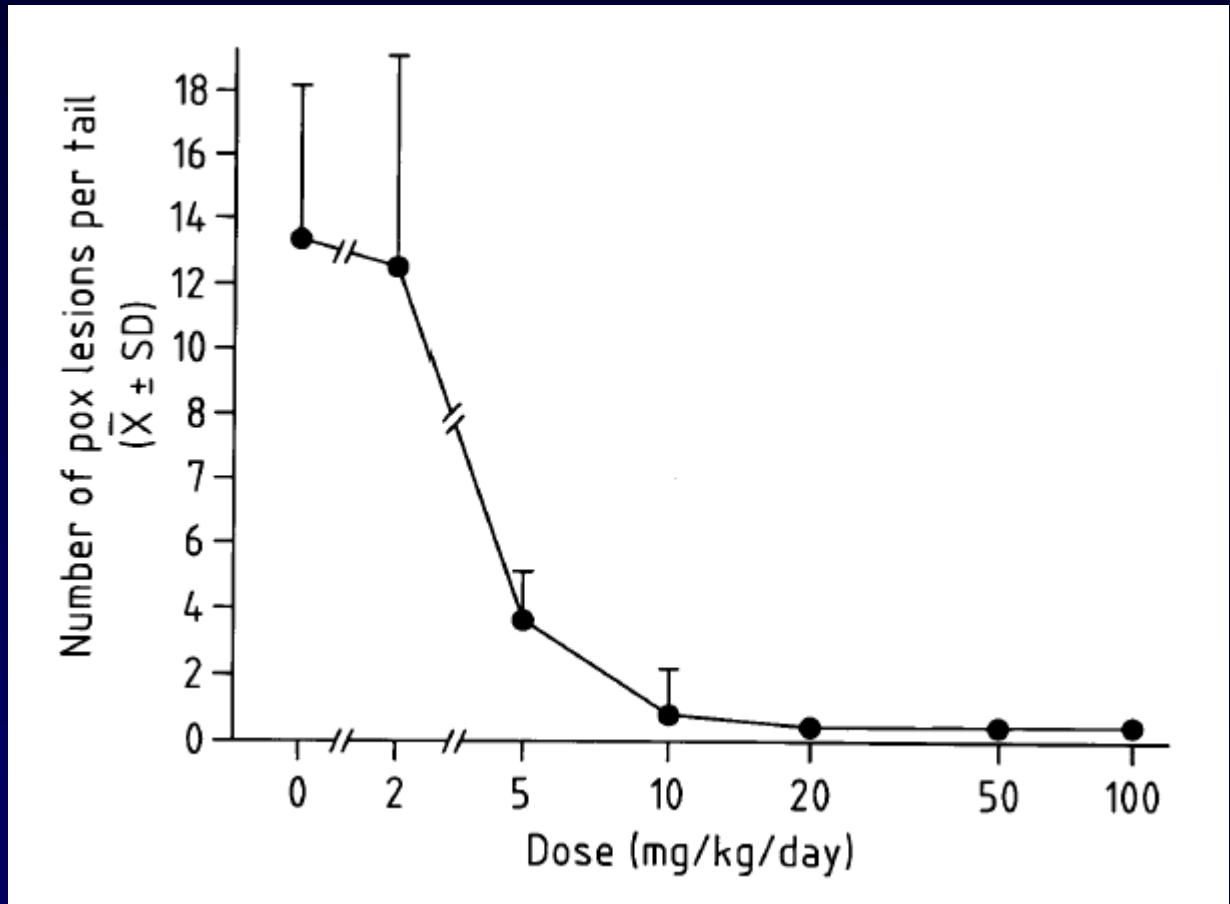
Activity of (*S*)-HPMPA analogues against herpes simplex virus (HSV-1, HSV-2, TK$^-$ HSV-1) and vaccinia virus (VV) in primary rabbit kidney cells

Compound	Minimum inhibitory concentration (µg/ml)*			
	HSV-1	HSV-2	TK$^-$ HSV-1	VV
(*S*)-HPMPA	2	4	2	0.7
(*S*)-cHPMPA	2	4	2	0.7
(*S*)-HPMPHx	> 400	> 400	> 400	> 400
(*RS*)-HPMPG	7	20	7	2
(*RS*)-HPMPDAP	10	20	10	2
(*S*)-HPMPC	4	10	2	4
(*S*)-HPMPT	70	70	> 400	300
(*RS*)-HPMPU	> 400	> 400	> 400	> 400
PMEA	7	7	7	150
PMEHx	> 400	> 400	> 400	> 400
PMEG	4	7	7	10
PMEDAP	2	0.7	1	20
PMEMAP	70	10	150	> 200

*Required to inhibit virus-induced cytopathogenicity by 50%.

De Clercq *et al.*, Antiviral Res. 8: 261-272 (1987)

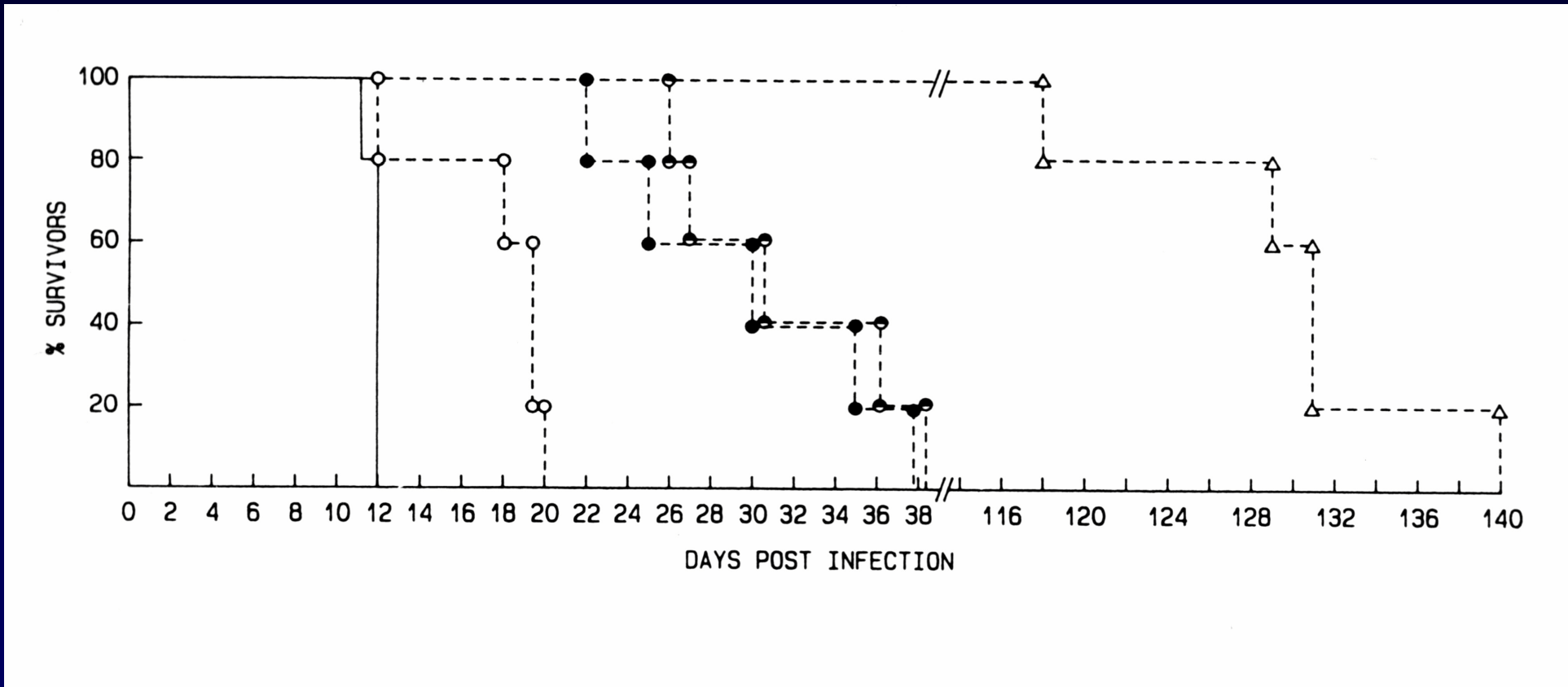
Inhibitory effects of (*S*)-HPMPA on tail lesion formation in NMRI mice inoculated i.v. with vaccinia virus



(*S*)-HPMPA was administered intraperitoneally for 5 days (starting 1 hr after infection) at the indicated doses. Pox tail lesions were enumerated at 7 days after infection

De Clercq *et al*., Antimicrob. Agents Chemother. 33, 185-191 (1989)

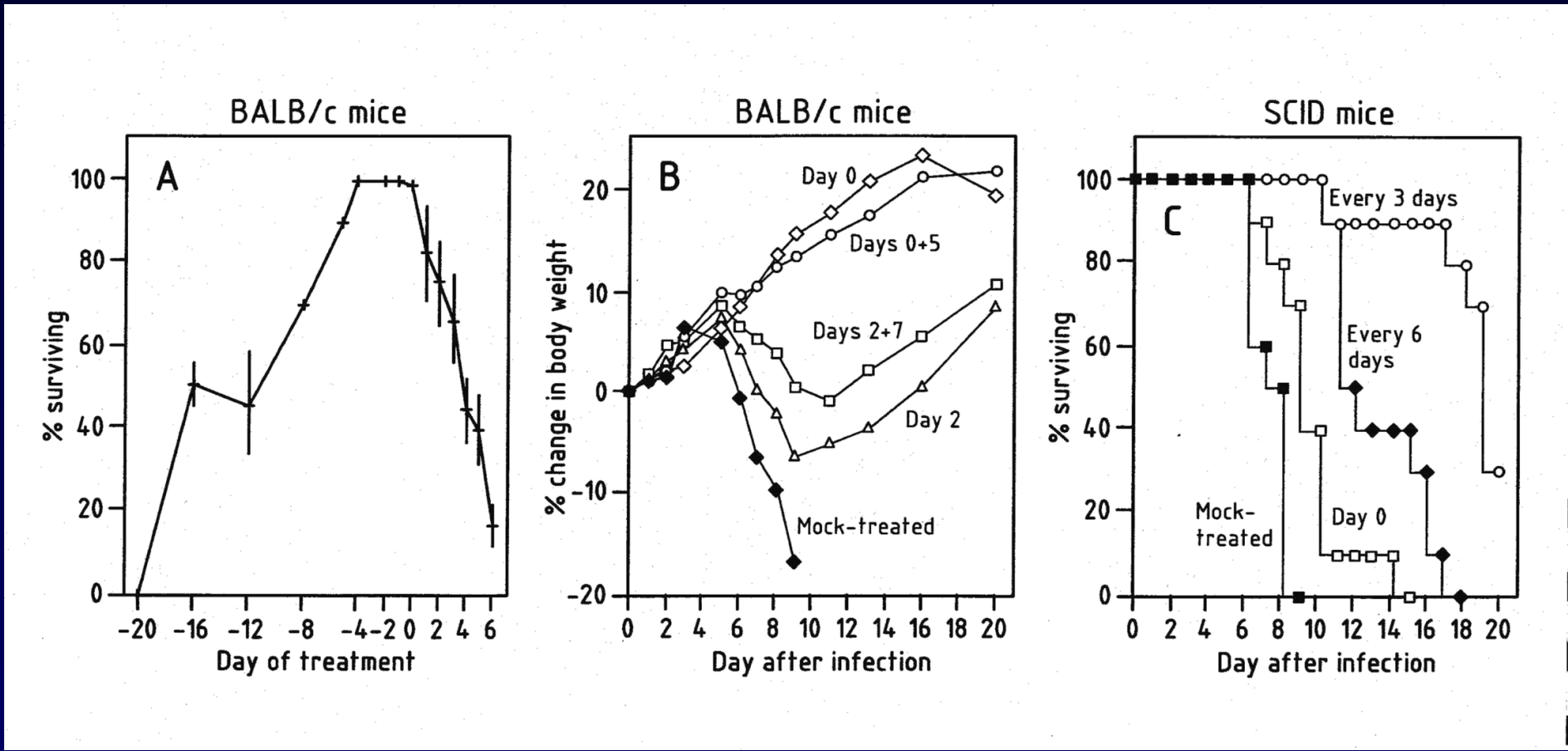
Survival of SCID mice infected i.v. with VV and treated s.c. with cidofovir



Treatment was initiated at 2 h after infection and was either continued for the next 4 days or repeated on day 4 p.i. and then twice every week (on day 1 and 4 of each week). Symbols: untreated controls (-) (n=5); treated at 1 mg/kg/day for 5 days (O) (n=5); at 5 mg/kg/day for 5 days (●) (n=5); at 20 mg/kg/day for 5 days (⊙) (n=5); or at 20 mg/kg/twice a week for up to 20 weeks (Δ) (n=5).

Neyts & De Clercq, J. Med. Virol. 41, 242-246 (1993)

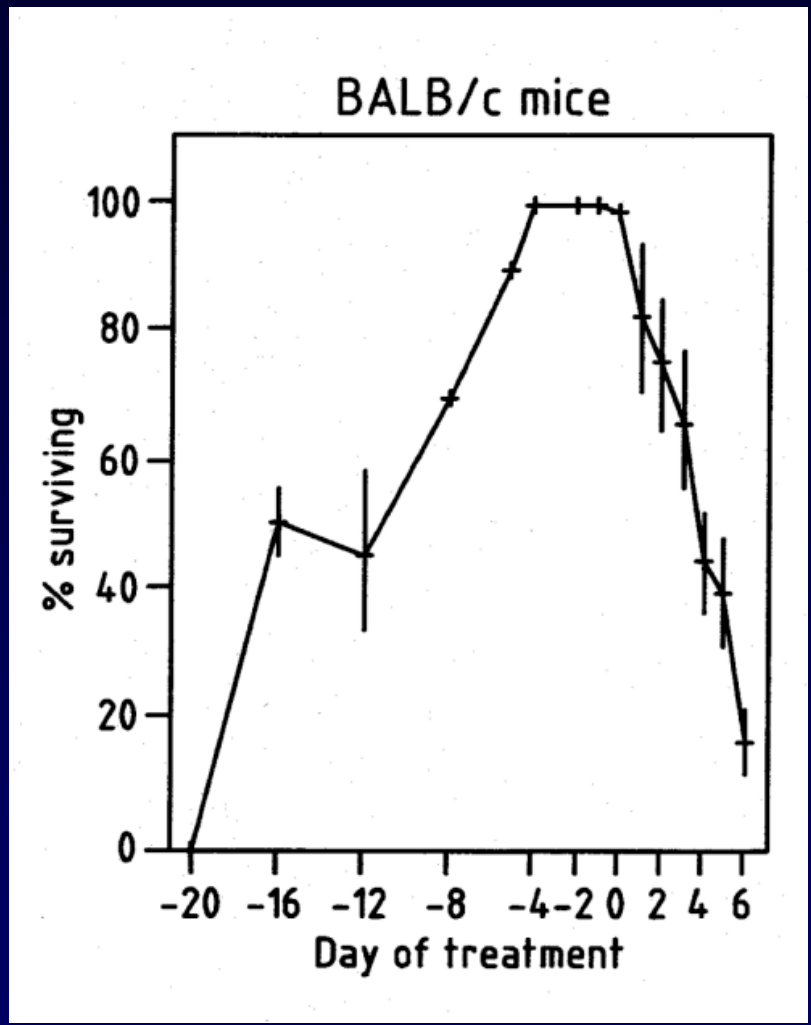
Intranasal cowpox virus infection



(A) Effect of a single s.c. injection of cidofovir (100 mg/kg) on survival.
(B) Effect of cidofovir (100 mg/kg on indicated days) on mean body weight.
(C) Effect of cidofovir (100 mg/kg on indicated times) on survival.

Bray *et al*., J. Infect. Dis. 181, 10-19 (2000)

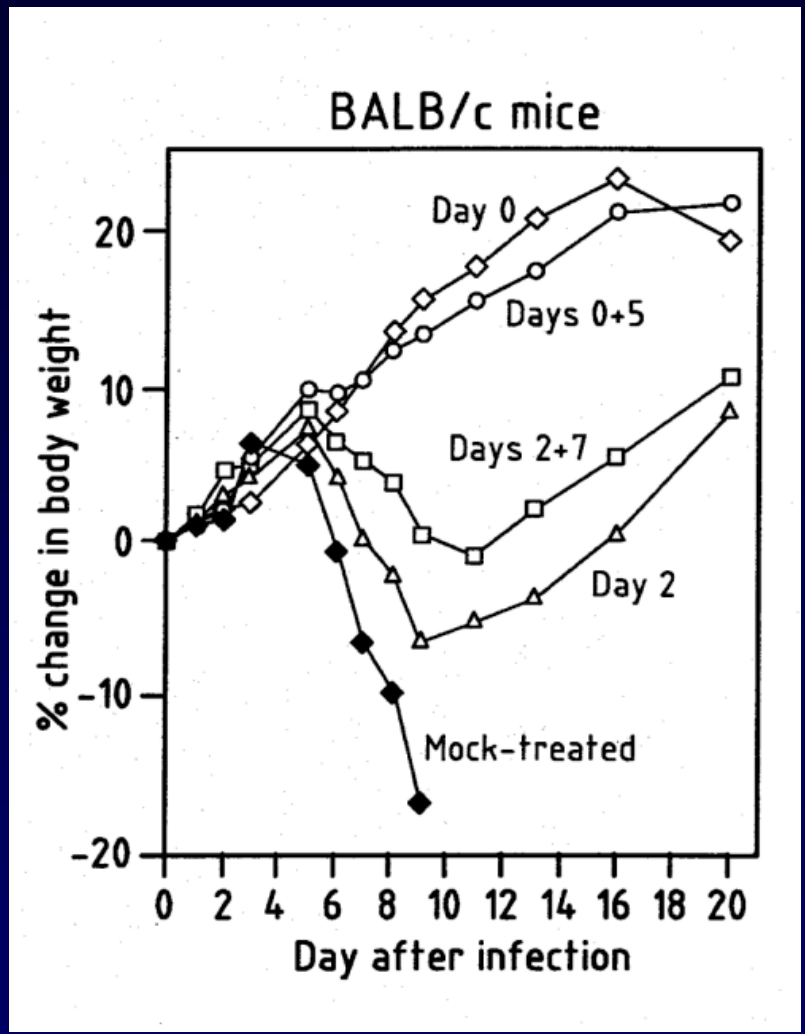
Intranasal cowpox virus infection



Effect of a single s.c. injection of cidofovir (100 mg/kg) on survival

Bray *et al*., J. Infect. Dis. 181, 10-19 (2000)

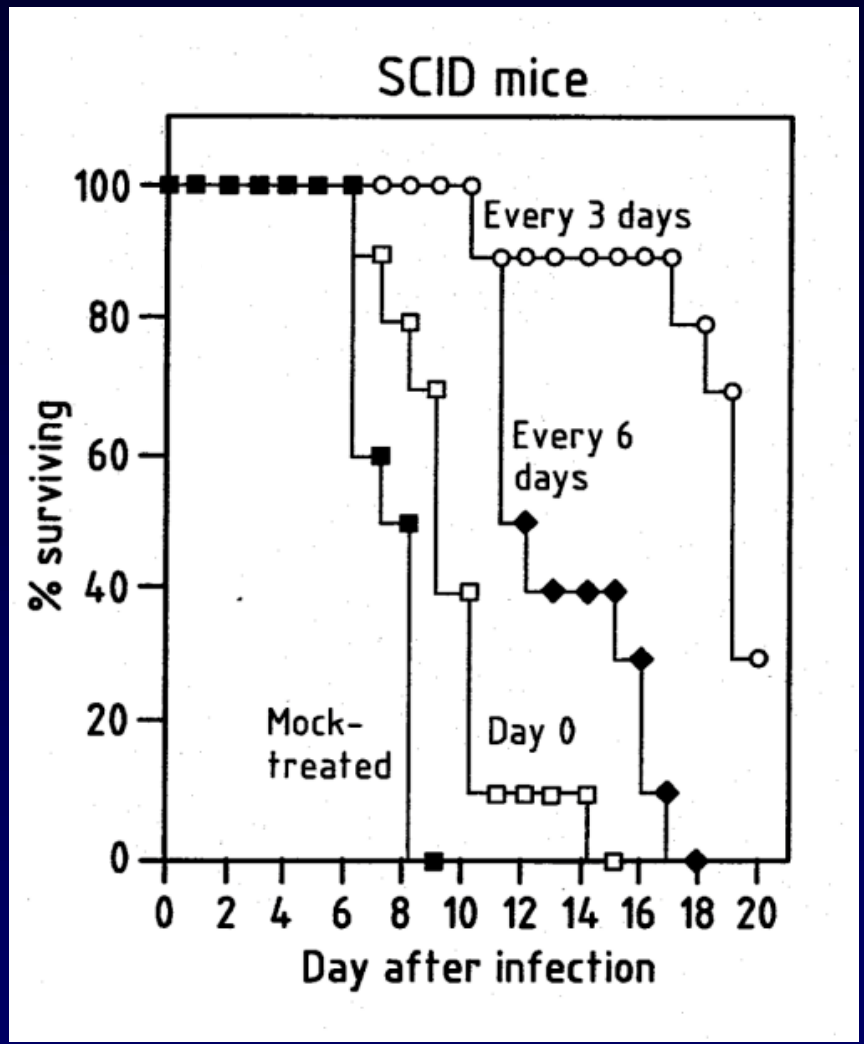
Intranasal cowpox virus infection



Effect of cidofovir (100 mg/kg on indicated days) on mean body weight

Bray *et al*., J. Infect. Dis. 181, 10-19 (2000)

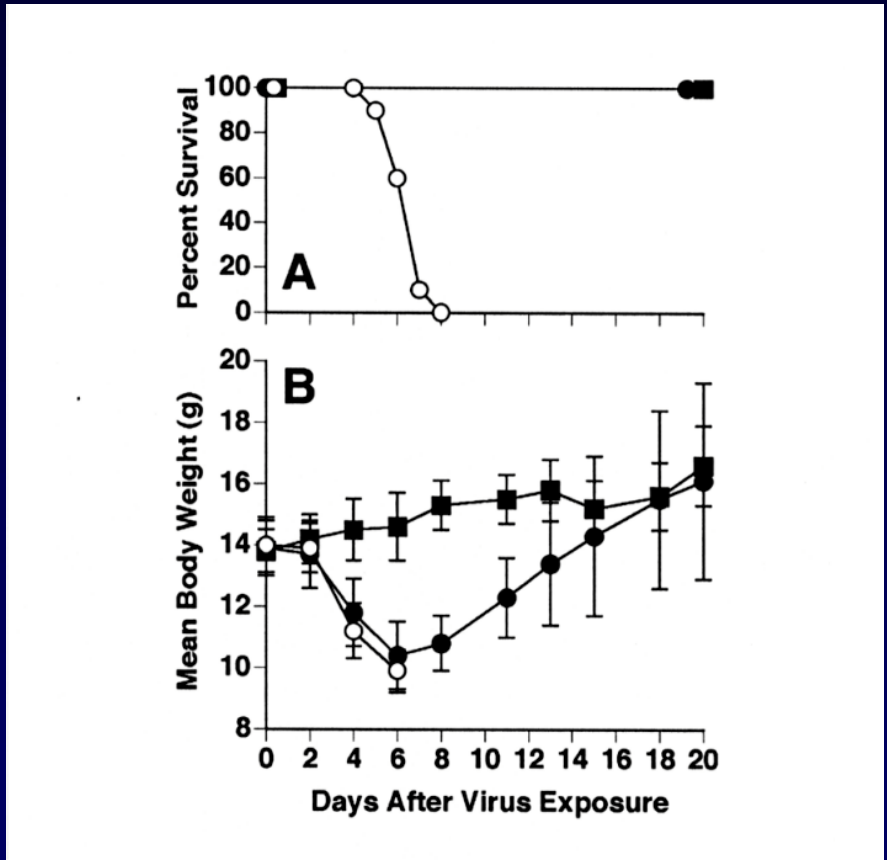
Intranasal cowpox virus infection



Effect of cidofovir (100 mg/kg on indicated times) on survival

Bray *et al*., J. Infect. Dis. 181, 10-19 (2000)

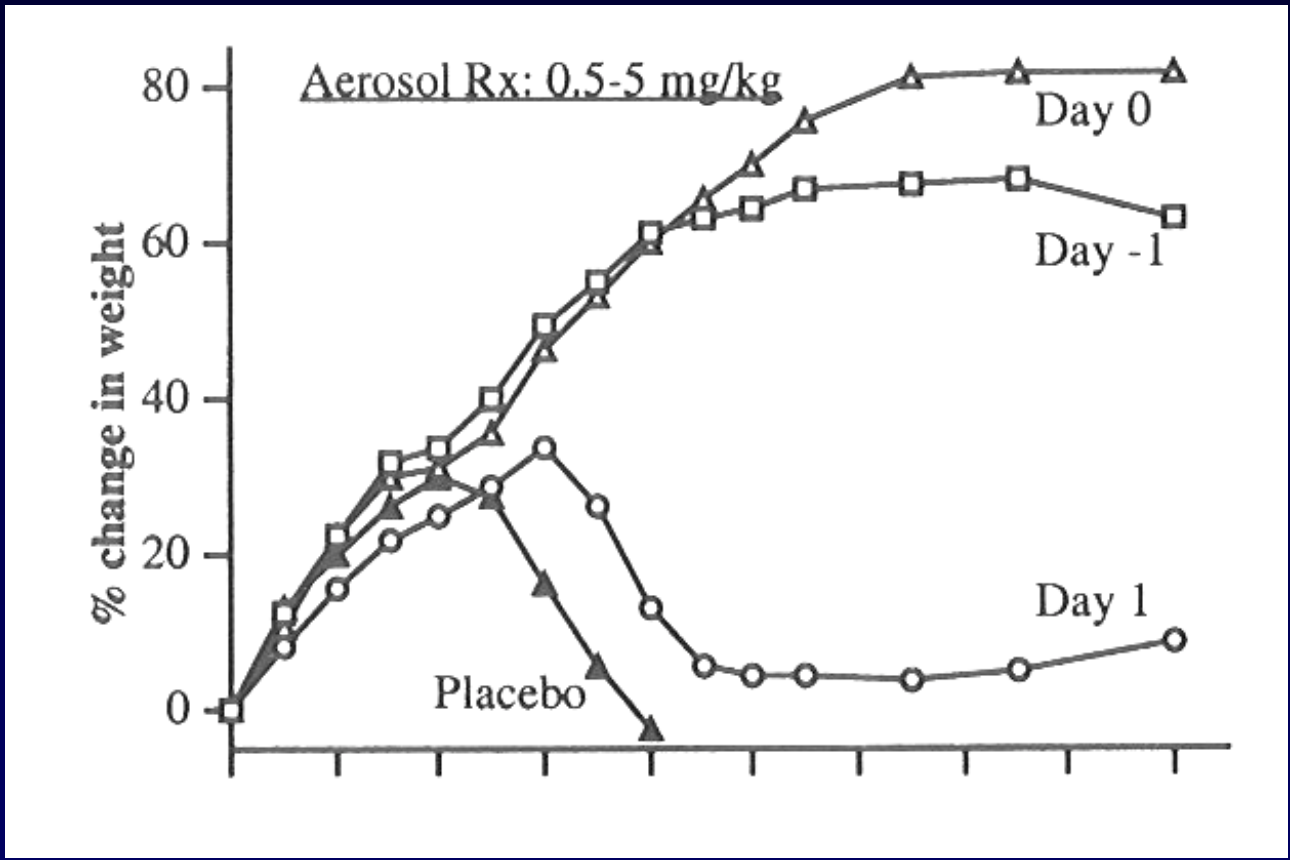
Effect of cidofovir treatment on survival (A) and on mean body weight (B) of BALB/*c* mice infected i.n. with vaccinia virus



A single i.p. injection of cidofovir (100 mg/kg) was given 24 h after virus exposure: (■) uninfected; (●) cidofovir; (O) placebo.

Smee *et al*., Antiviral Res. 52, 55-62 (2001)

Treatment of aerosolized cowpox virus infection in mice with aerosolized cidofovir



Change in mean body weight of BALB/c mice infected by aerosolized cowpox virus and treated with aerosolized cidofovir (0.5-5 mg/kg) on day –1, 0 or 1.

Bray et al., Antiviral Res. 54, 129-142 (2002)

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Special Issue

Viral Bioterrorism and Biodefense

Guest Editors
E. De Clercq
E.R. Kern

0166-3542(20020601)54:3;1-B

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(continued from outside back cover)