


**Global Advisory Committee on  
Vaccine Safety  
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**Adverse Events  
following Smallpox  
Vaccination**

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# “Vaccine” development

- Variolation
- 1798 Jenner’s “variolae vaccinae”
- Animal skin derived vaccine pulp and lymph

1950s

Attempts for standardisation

1956

First production in eggs

1960s

First production in tissue culture

1969

Principle of seed lots introduced

NB:

No efficacy testing in controlled trial setting



# Vaccinia strains



- Some widely used strains in the eradication era and their pathogenicity (Marennikova, 1969)

High:	Temple of Heaven	(China)
	Copenhagen	(Denmark)
	Ikeda, Dairen	(Japan)
	Tashkent	(USSR)
Moderate:	Bern	(FR Germany)
	Patwadangar	(India)
	Lister	(UK)
Low:	EM-63	(USSR)
	NYCBH	(USA)

# Mild to moderate AEFIs

- Local Reactions
  - Pain at vaccination site (up to 85%)
  - Satellite lesions
  - Large vaccination reactions (10%)  
“robust takes”



# Mild to moderate AEFIs

- Brief Systemic Reactions
  - Regional lymphadenopathy (up to 55%)
  - Fatigue (up to 50%)
  - Headache (up to 45%)
  - Myalgia and chills (up to 20%)
  - Nausea (up to 15%)
  - Fever  $\geq 37.7^{\circ}\text{C}$  (up to 10%)
  - Non-specific rash (up to 10%)



# Mild to moderate AEFIs

- Inadvertent Inoculation (530 per million vaccinees)
  - Eye, vulva, perineum
  - May require therapy to prevent vaccinia keratitis



# Mild to moderate AEFIs

- Generalised Vaccinia (GV)  
(240 per million vaccinees)
  - Disseminated maculopapular or vesicular rash in otherwise healthy vaccinees
  - Usually self-limited, generally benign
  - Severe cases may require VIG



# Mild to moderate AEFIs

- Erythema Multiforme (EM) (131 per million vaccinees)
  - Hypersensitivity reaction to virus
  - Pruritic macular or papular rash
  - Lasting up to 4 weeks



## Mild to moderate AEFIs

- AEFI in contacts of vaccinees (27 per million vaccinees)
  - 60% inadvertent inoculation
  - 30% Eczema vaccinatum  
(may be more severe in contacts)



# Serious AEFIs

- Eczema Vaccinatum (EV) (10-39 per million vaccinees)
  - In persons with history of atopic dermatitis
  - Localised or generalised rash
  - Often systemic illness
  - Usually requires treatment with VIG
  - Case fatality rate up to 6%



# Serious AEFIs



- Postvaccinial Encephalopathy/Encephalitis (PVE)  
(3-12 per million vaccinees)
  - Acute toxic encephalopathy (ATE)
  - Most common in infants
  - Headache, fever, altered mental status, lethargy, seizures, hemiplegia, aphasia, coma
  - In 25% of survivors residua of mental impairment
  - Case fatality rate 15-30%

# Serious AEFIs



- Postvaccinial Encephalomyelitis (PVEM)  
(3-12 per million vaccinees)
  - Acute disseminated encephalomyelitis (ADEM)
  - Most common in children > 2 years
  - Headache, fever, malaise, vomiting, somnolence, disorientation, convulsions, coma
  - In some survivors mental impairment and paralysis
  - Case fatality rate 10-35%

# Serious AEFIs

- Progressive Vaccinia (PV)  
(1-1.5 per million vaccinees)
  - In persons with cellular immunodeficiency
  - Progressive necrosis at vaccination site with metastases
  - Need tertiary-level supportive care including VIG therapy
  - Case fatality rate up to 45%



# Serious AEFIs

- Fetal Vaccinia (PV) (~50 cases worldwide)
  - Vaccinia transmission from mother to fetus
  - Skin lesions, organ involvement
  - Often fetal or neonatal death



# Serious AEFIs



- Death (1-2 per million primary vaccinees)
- Mostly as a result of PVE (52%)
  - PV (28%)
  - EV among contacts (18%)

# Therapy



- Vaccine Immune Globulin (VIG)
  - For severe GV, EV, certain cases of PV
  - Not indicated in PVE
  - Contraindicated in vaccinia keratitis
- Cidofovir (Vistide TM)
  - Second line, to be given with probenecid
  - Nephrotoxic and potentially carcinogenic
  - Under investigational drug protocol

# Contraindications



- In eradication era:
  - Immune disorders
  - Eczema
  - Pregnancy
  - Disorders of the CNS

# Postvaccinial Encephalitis (PVE)

Country	Strain	Time	N	Incidence per million	Mortality per million
NL	Copenhagen	1924-44	803,484	173.0	66.0
UK	Lister?	1924	4,275,109		24.0
UK	Lister?	1930		20.0	
Germany	Hamburg?	1930		10.0	
NL	Copenhagen?	1931-32		200.0	
NL	Copenhagen	1946-58	2,664,592	37.5	4.5
USA/NYC	NYCBH?	1947	5,000,000	9.0	0.8
UK	Lister?	1951-70	16,000,000	9.4	2.3
NL (>2 yr)	Copenhagen	1959-63		250.0	
NL (>2 yr)	Lister	1964-68		0.0	
NL	Copenhagen	1959-63	1,050,000	33.0	19.0
NL	Lister	1964-68	1,050,000	13.0	12.0
USA	NYCBH	1968	6,244,000	2.9-12.3	0.7
USSR	Tashkent	1969		46.0	
USSR	EM-63	1969		7.0	

# Progressive Vaccinia (PV)

Country	Strain	Time	N	Incidence per million	Mortality per million
E & Wales	Lister?	1951-60	5,000,000	1.6	1.4
UK	Lister?	1951-70	16,000,000	1.1	0.8
USA	NYCBH	1968	6,244,000	0.9-1.5	0.4

# Eczema Vaccinatum (EV)

Country	Strain	Time	N	Incidence per million	Mortality per million
USA/NYC	NYCBH?	1947	5,000,000	9.0	
UK	Lister?	1951-70	16,000,000	4.5	0.7
S Wales	Lister?	1962-63	900,000	11	2.2
Sweden	Sweden	1963	300,000	23.3	
USA	NYCBH	1968	6,244,000	10.4-38.5	
Japan	LC16m8	1975	40,000	25.0	
Israel	Lister?	1991-96		15.0	0.0

# Carditis



Country	Strain	Time	N	Incidence per million	Mortality per million
Sweden	Sweden	1963	300,000	23.3	

# Generalised Vaccinia

Country	Strain	Time	N	Incidence per million	Mortality per million
E & Wales	Lister?	1951-60	5,000,000	32.4	
USA	NYCBH	1968	650,000	242.0	
Japan	LC16m8	1975	40,000	200,0	
Israel	Lister?	1991-96		9.0	0.0

# Inadvertent Inoculation (eye)

Country	Strain	Time	N	Incidence per million	Mortality per million
France		1953	850,000	22.4	
S Wales	Lister?	1962-63	900,000	12.2	

# AEFI Incidence and mortality (range)

AEFI	Time period	Incidence per million	Mortality per million
PVE (all countries)	1924-73	0 – 250.0	0.7 – 66.0
PV (all countries)	1951-70	0.9 – 1.6	0.4 – 1.4
EV (all countries)	1947-96	4.5 – 38.5	0 – 2.2
All serious (USA)	1963	9.4	0.5
All serious (USA)	1968	14.2 – 52.3	1.1 – 1.5
GV (all countries)	1968-96	9.0 – 242.0	0
All mild/moderate (USA)	1968	935.0	0

# **AEFI Incidence and mortality USA 1968 (NYCBH strain)**



- Serious AEFI 14 - 52 per million primary vaccinees
- Mild / Moderate AEFI 935 per million primary vaccinees
- Deaths 1 - 2 per million primary vaccinees

# **AEFI incidence and mortality estimation Universal Vaccination USA 2003**



1949-72: 3000 serious AEFI, 150 deaths

1970-00: 210 deaths projected (Lane et al, 1969)

USA 2003: 1600 serious AEFI, 190 deaths (1-29 years vaccinated)

USA 2003: 4600 serious AEFI, 285 deaths (1-65 years vaccinated)

NB: 25% of population excluded from vaccination:

10% due to eczema

5% due to immunodeficiency

10% household contacts with these conditions

(Kemper et al, 2002)

# Vaccines



- Calf-lymph derived vaccinia from the eradication era
  - Dryvax TM NYCBH strain (Wyeth) - 1856 England
  - Aventis NYBCH strain (Aventis) - as above
  - Lancy Vaxina Lister Elstree (Berna Biotech) - 1870 Cologne
  - EM-63 (Russia) - from NYCBH strain via Ecuador
  - G-9 (China) - from Tientan (Temple of Heaven) strain

# Vaccine developments



- Tissue culture vaccinia strains
  - ACAM 1000 NYCBH in MRC5 cells (Acambis)
  - ACAM 2000 NYBCH in Vero cells (Acambis/Baxter)
  - Bilthoven Attenuated Lister in rabbit kidney cells
  - Elstree BN Lister in chick embryos (Bavarian Nordic)
  - LC16m8 Attenuated Lister in rabbit kidney cells (Japan)
  - LC16-Kaketsuken Derived from LC16m8 (Japan)
  - CVI-78 NYCBH 124 x in chick embryos
  - CVII NYCBH 235 x in chick embryos (NL)

# Vaccine developments



- Highly attenuated orthopox and aviviruses
  - MVA Modified Ankara 572 x in chick embryos (BN)
  - NYVAC Attenuated Copenhagen (Connaught/Aventis)
  - TROVAC Fowlpox virus
  - ALVAC Canarypox virus