

Smallpox Vaccine



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Smallpox Vaccine

- Original material used by Jenner was probably cowpox
- Vaccine constituent changed from cowpox to vaccinia during the 19th century

Vaccinia Virus

- Origin of vaccinia virus unknown
- Genetically distinct from cowpox and variola
- May be a virus now extinct in nature

Vaccinia Virus

- Multiple strains with different levels of virulence for humans and animals
- U.S. vaccines (Wyeth Dryvax, Acambis, Dynport, Aventis-Pasteur) contain New York City Board of Health (NYCBOH) strain

Vaccinia Virus

- NYCBOH “strain” now known to be a “soup” of genetically closely related strains.
- “plaque purification” for Acambis seed virus.

Vaccine Preparations

- **Glycerinated lymph in capillary tubes, required careful refrigeration.**
- **Vaccine has been made on calf skin, egg CAM, tissue culture, rabbit skin, etc.**

Vaccine Production

- Liquid vaccine lost potency in tropical climates
- Freeze-drying technology developed in 1909
- Improvements by Collier in early 1950s produced vaccine stable at 37°-45° C for 64 weeks

Wyeth Dryvax Vaccine

- **Lyophilized NYCBOH vaccinia containing calf lymph**
- **Diluent provided in separate syringe-like vial with attached needle, injected into the vaccine vial.**
- **Contains trace amounts of polymyxin B, streptomycin, chlortetracycline and neomycin**

Vaccine Potency

- US lyophilized vaccines have a titer of at least 10^8 pfu/ml.
- Past vaccine with titers of as little as 10^6 gave good takes.
- Frey's study of 1:10 diluted Dryvax, NEJM 2002.

Response to Vaccination

- **Neutralizing antibody:**
 - 10 days after primary vaccination
 - 7 days after revaccination
- **Considered fully protected after a successful response demonstrated at vaccination site**

Vaccine Efficacy

- **Clinical efficacy estimated in household contact studies**
- **91%-97% reduction in cases among contacts with vaccination scar**
- **Studies did not consider time since vaccination or potency of vaccine**

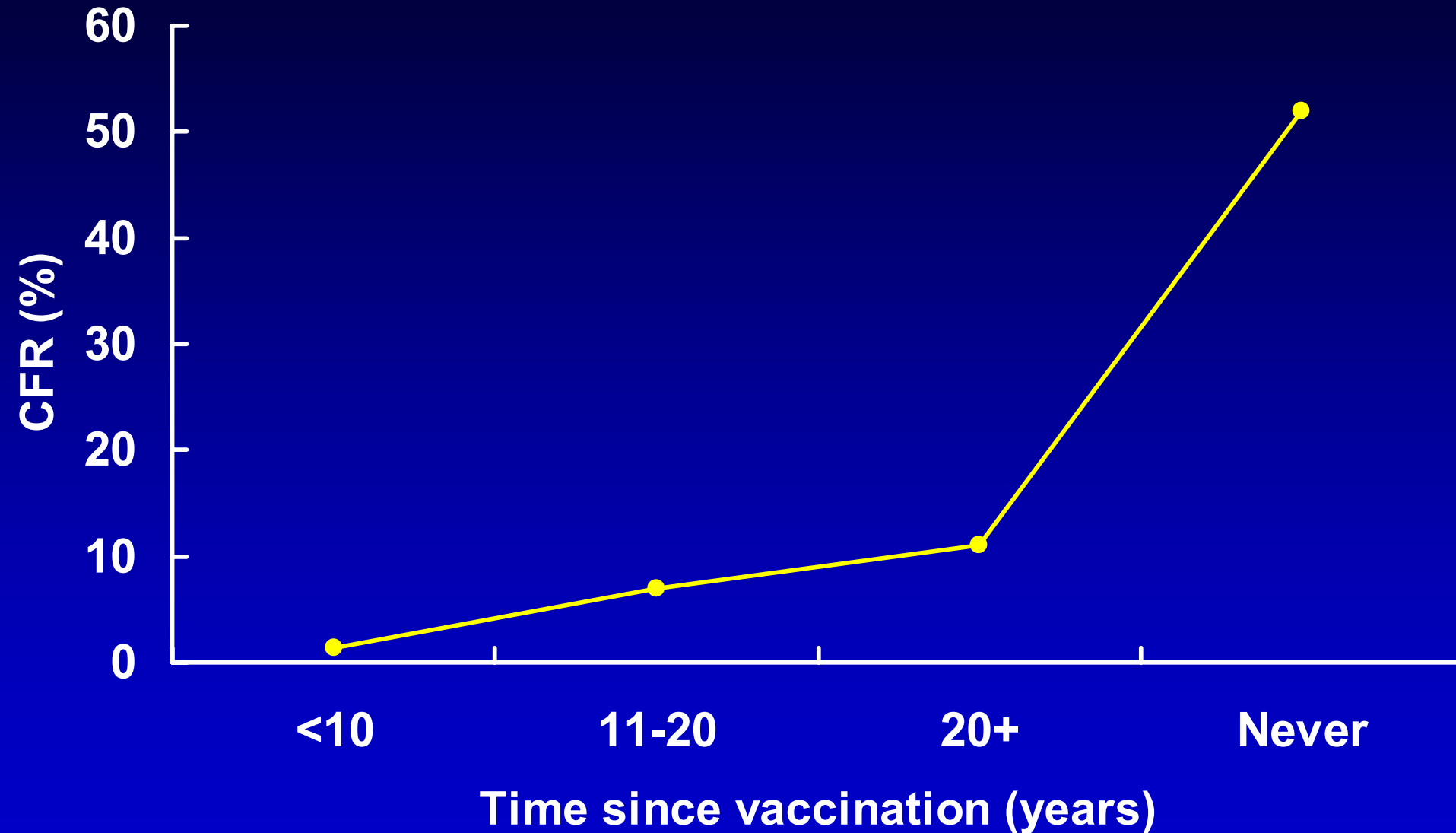
Post Exposure Vaccine Efficacy

		% with smallpox
Madras	Postexp vacc	29.5
	Never vacc	47.6
Pakistan	Vacc \leq10 days	75.0
	Never vacc	96.3
Pakistan	Vacc \leq7 days	1.9
	Never vacc	21.8

Duration of Immunity

- High level of protection (~100%) for 3 years following vaccination
- Substantial but waning immunity for ≥ 10 years
- Reduction in disease severity

CFR by vaccination status, Europe, 1950-1971



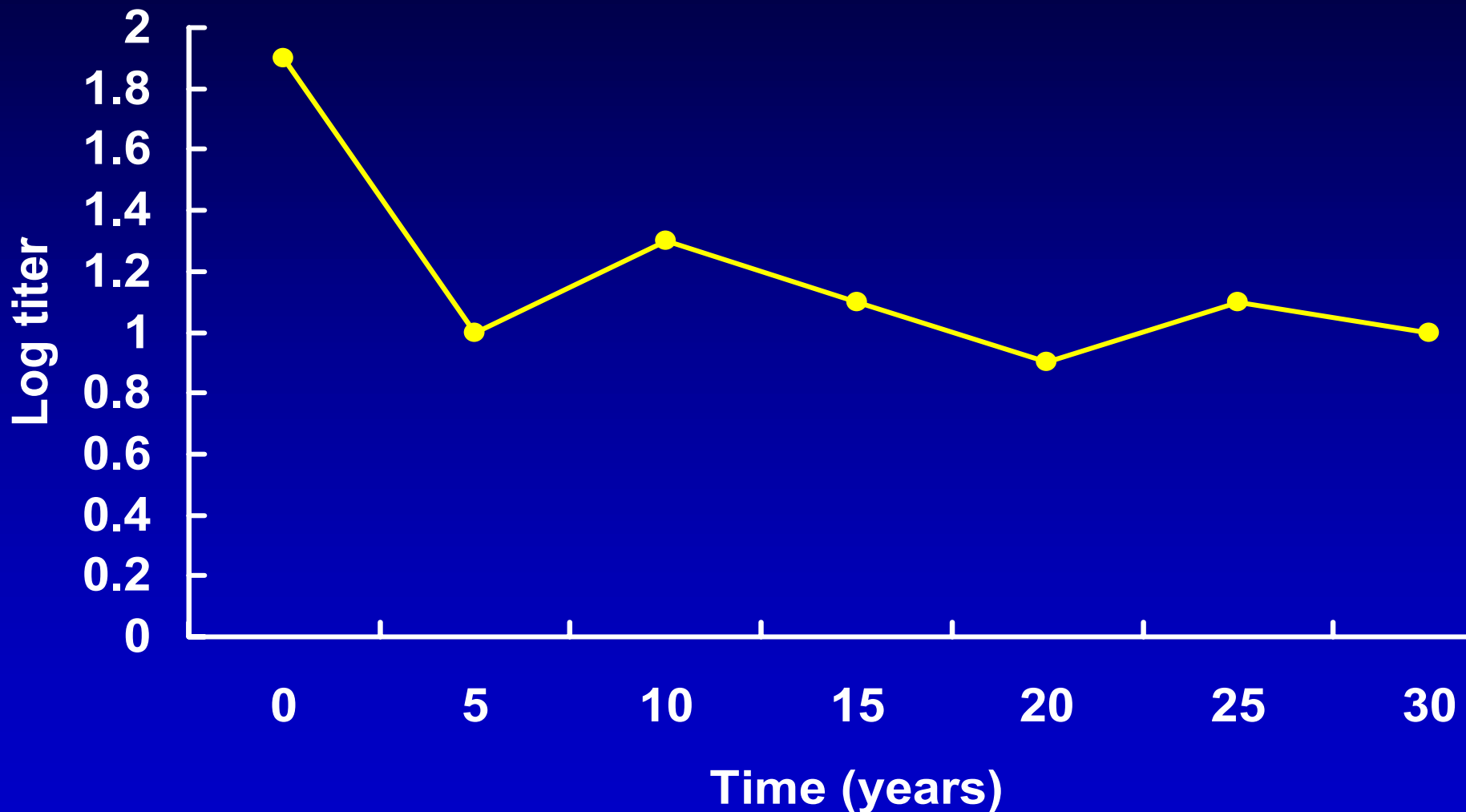
Cases and deaths after importations of smallpox into Europe



Antibody Persistence

- Level of antibody that protects against smallpox infection unknown
- Neutralizing antibody $\geq 1:10$ persists up to 30 years following 3 doses

Antibody Persistence Following Second Revaccination



Baruch El-Ad, et al J Infect Dis 1990;161:446-8.
Subjects vaccinated on 0, 8, 18 year schedule

immunity

- **Similar to Neuts; 30 years or more.**
- **Protective level unknown.**
- **Demkowicz et al. J. Virology 1996
Human cytotoxic T-cell memory: long-lived response to vaccinia virus.**

persistence of immunity

- **Recent review of data from outbreaks in Boston, Liverpool, in 19th Century.**
- **CFR down 30 years post vaccination.**
- **Cohen J. Science 2001 Smallpox vaccination: how much protection remains?**

Vaccination site

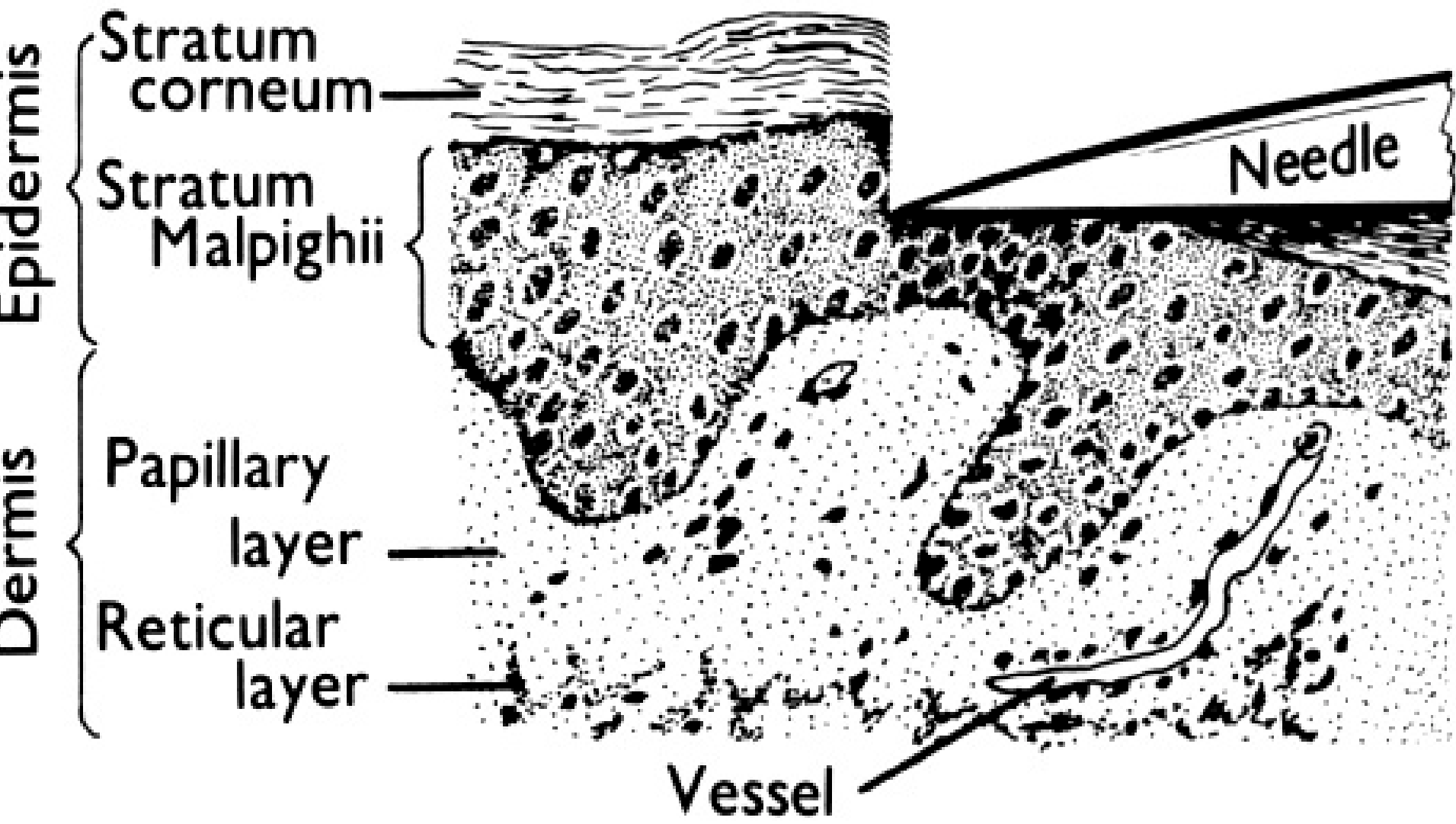
- Many have been used. (thigh, back, buttock).
- Deltoid insertion by ease of access, tradition, difficulty in scratching etc.
- Revaccination in the old scar.

Vaccination technique

- Many types of knives, scalpels, needles, vaccinostyles used to insert virus into the skin.
- Virus on intact skin won't "take".
- Virus injected IM won't "take".

Vaccination technique

- **By 1966 in US, multiple pressure and jet injection were major methods**
- **1967, introduction of the bifurcated needle**



Vaccination technique

- Prior to administration, please refer to package insert for the **number** of needle punctures to administer.
- Needle picks up the right dose of vaccine between the prongs by capillary action.
- 3 or 15 swift firm strokes in the same spot.
- Should get slight ooze of blood or serum at 20-30 seconds.

Vaccination technique

- **Site preparation: NONE!!!!**
- **Alcohol inactivates vaccine.**
- **Ether or acetone dissolves skin lipids, and probably promotes satellite lesions.**
- **Warm water if necessary.**

Vaccination site management

- **Controversial.**
- **No dressings in the old days.**
- **Loose gauze, long sleeves, to pick up exudate.**
- **Cover loose gauze with Opsite.**
- **Avoid maceration by occlusive dressings.**

Clinical Response to Vaccination

- “Jennerian vesicle” at inoculation site
- Swelling and tenderness of axillary lymph nodes, usually during 2nd week
 - 15%-20% of primary vaccinees
 - 0%-15% of revaccinees
- Fever and malaise common

Clinical Response to Vaccination*

Symptom/sign	Time after Vacc
Papule	3 days
Vesicle	5-6 days
Pustule	7-11 days
Maximum erythema	8-12 days
Scab	14 days
Scab separation	21 days

*typical response in a nonimmune person

Clinical response to vaccination

- **VIG doesn't blunt the normal response to vaccination.**
- **Dermal response usually normal in agammaglobulinemics.**
- **Evidence of cellular immunity by about day 8.**

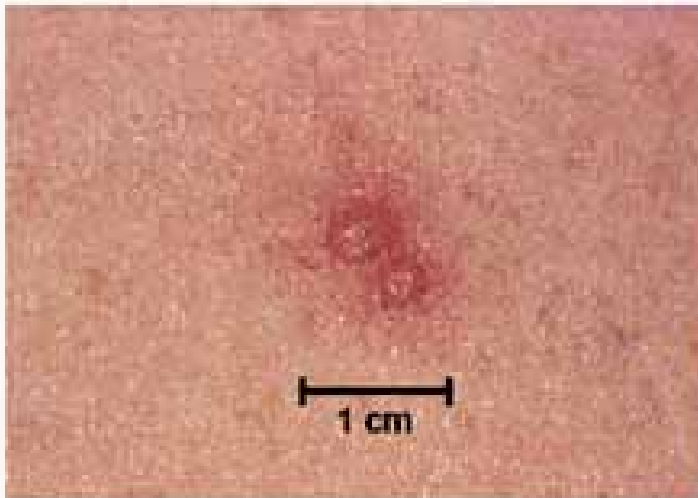
Antibody response to vaccination

- Neutralizing antibodies by about day 8.
- HAI's about day 8 or 9, unknown significance.
- CF's about day 8 or 9, unknown significance.

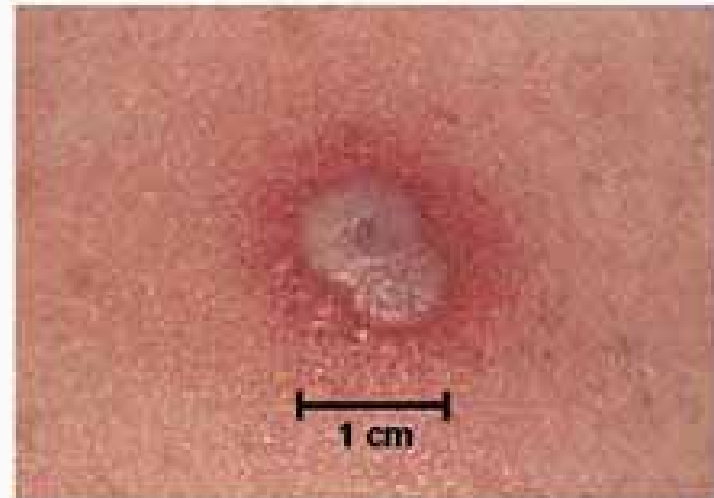
Normal primary vaccination

- Strain differentials.
- NYCBOH most “gentle” strain.
- Lister strain common in Europe, Israel.
- “Robust” responses more common, data poor.
- Viremia, tonsilitis, etc.
- Satellite lesions are normal and self-limited

Primary Vaccination Site Reaction



Day 4



Day 7



Day 14



Day 21

Normal progression of vaccination site



**Normal progression of vaccination site
Day 7**



**Normal progression of vaccination site
Day 12 – note heaped up border
and pustule drying from center outward**

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Satellite Lesions

Local Skin Reactions

- Allergic reactions to bandage and tape adhesives
- Maceration
- Robust takes (aka large local reactions)
- Bacterial superinfections

Local Reactions to Adhesive

- Erythema or vesicles correspond to placement of adhesive tape
- No systemic symptoms
- Steroid treatment not recommended

Local allergic reactions

- **Consider prescreen for history of sensitivity**
- **Treatment**
 - **Rotate bandage and tape**
 - **Alternative adhesive products**
 - **Bandage holiday**



**Erythema in 2 different
first-time vaccinees
day 5 post-vaccination**



**Vesicle at edge of adhesive drsg:
Negative viral culture no
progression to pustular stage**

Circle one: (Vac #1) / Vac #2

“Robust” takes

- Case definition from CDC experience:
 - > 3 inches of redness, swelling, pain and warmth
- About 2% to 16% of normal adult NYCBOH “takes:
- Onset 8-10 days (differs from bacterial infxn <5 days > 15 days)
- Symptoms usually improve 24-72 hrs



**Robust Take with lymphangitis:
Extensive erythema and induration
with linear streak posteriorly on Day 9**

“Robust” takes

- Probably less in children.
- Not uncommon in revaccinees whose primary was >30 years previously.
- Do not confuse with early progressive vaccinia.

Robust Takes (RT) Therapy

- **Observe carefully**
- **Supportive therapy**
 - **Rest affected limb**
 - **Analgesia (non-aspirin)**
 - **NSAIDs**

Robust Take



Bacterial Infection



Robust take vs Bacterial superinfection

Note the impetiginous changes

Secondary Bacterial Infection

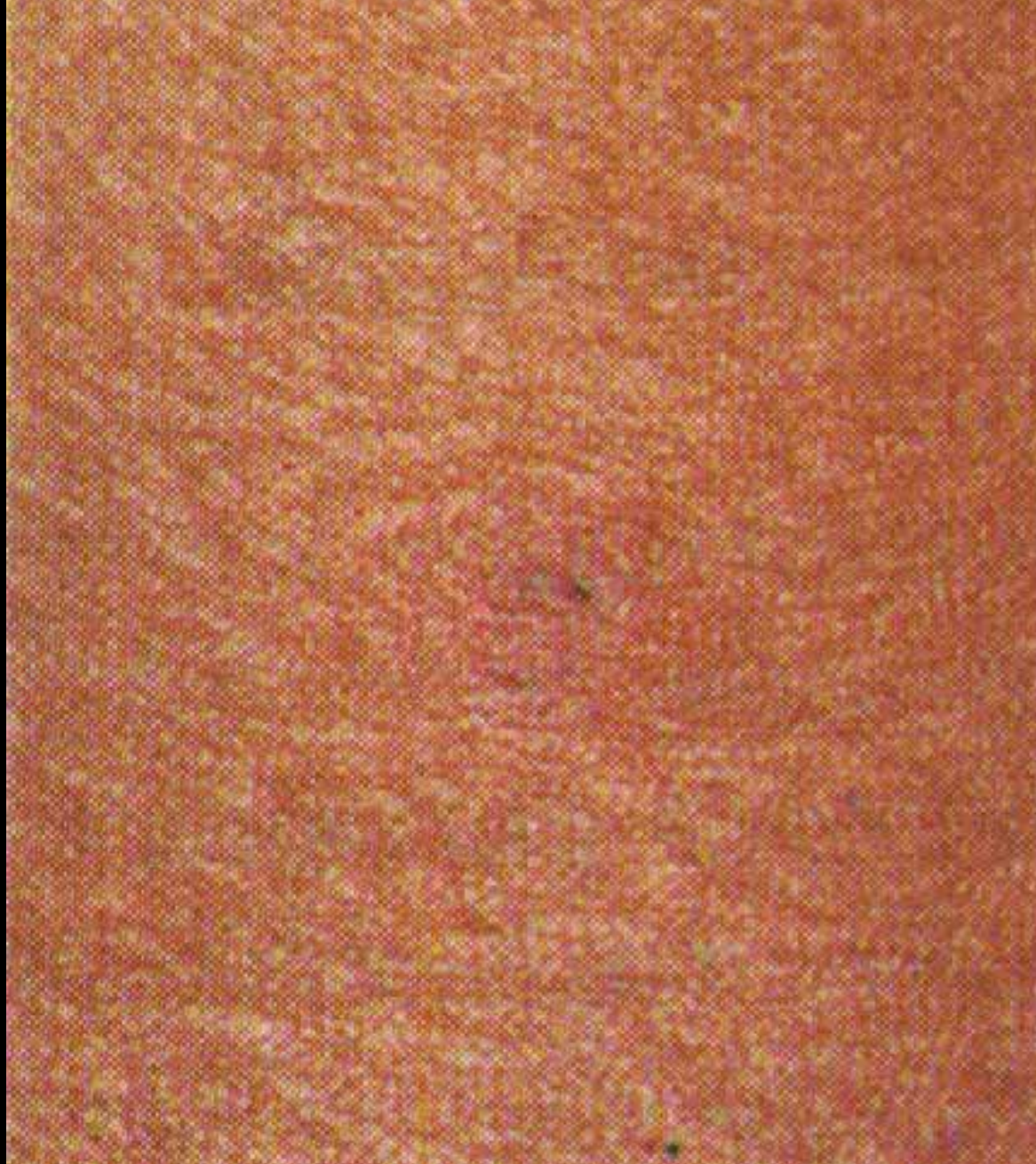
- More common among children than adults
- Usually *Staphylococcus aureus* or Group A beta hemolytic Streptococci
- Anaerobic and mixed infections may occur
- Evaluate with gram stain and culture
- Antibiotic therapy based on culture

Clinical Response to Vaccination

- **Major (primary) reaction**
 - Indicates viral replication has occurred and vaccination was successful
- **Equivocal reaction**
 - Indicates immune suppression of viral replication or allergic reaction without production of immunity

Major Reaction (6-8 days after vaccination)

- Vesicular or pustular lesion
- Area of definite palpable induration surrounding a central crust or ulcer
- Indicates viral replication



Primary vaccination, day 3



Primary vaccination, day 7



Primary vaccination, day 10



Primary vaccination, day 14

First-time vaccinee day 6, 10 & 15



Revaccinee day 4, 8, 10 & 15

Comparison of Major reaction
by vaccination status



Equivocal Rxn i

Equivocal Reaction

- **All responses* other than major reactions**
- **Caused by immunity, insufficiently potent vaccine, vaccination technique failure**
- **Vaccination should be repeated with another vial, if possible**

***Includes accelerated, modified, vaccinoid, immediate, early, or immune reactions.**

Equivocal Reaction

- **Immediate reaction**
 - **Delayed-type hypersensitivity to vaccine component (erythema only)**
 - **Occurs 24-48 hours after vaccination**
 - **No immunity**

Older terminology

- Accelerated reaction, reaction of immunity, vaccinoid reaction, modified take.
- All attempted to describe take with viral replication, accelerated by residual immunity.

Current terminology

- **Either “Major” or “Equivocal”.**
- **Can only read at 6-8 days.**
- **True equivocals should be rare now with most people not vaccinated for 30 years +**

Take Rates

- Influenced by many factors:\ul>- Vaccine (titer etc.)
- Method
- Vaccinator
- Immunity level in vaccinees
- Training

Take Rates

- **Should approach 100% in primaries.**
- **Was about 70% in 1960's revaccinees.**
- **Should approach 100% in today's revaccinees who have minimal immunity.**

Transmission of Vaccinia

- **Vaccinia virus may be recovered from the site of vaccination from development of papule (2-5 days) until scab separates from the skin**
- **Day 3 to day 19, highest shedding at day 6-9.**
- **Data are minimal.**

Transmission of vaccinia

- **Uncommon, generally direct close contact.**
- **No evidence for respiratory spread (despite Russian data)**
- **10-30 contact transmissions per million primary vaccinations.**

Transmission of vaccinia

- **Very few health care workers have spread vaccinia (4 documented US cases).**
- **Mostly to patients with atopic dermatitis.**
- **Neff et al JAMA 2002.**

Transmission of vaccinia

- Nosocomial spread of vaccinia.
- All pre-modern infection control
- Almost certainly spread via health care workers with careless hand-washing procedures.
- Sepkowitz NEJM Jan 2003

Smallpox Vaccine Products

Overview

- **Wyeth Dryvax (1:1 & 1:5)**
- **Acambis Vaccinia Vaccine in MRC5 Cells (Acam1000)**
- **Acambis Vaccinia Vaccine in Vero Cells (Acam2000)**
- **Aventis Pasteur Vaccine**

Chimpanzee Vaccine Supply and Production

Acam 1000

~54 million doses

Acam 2000

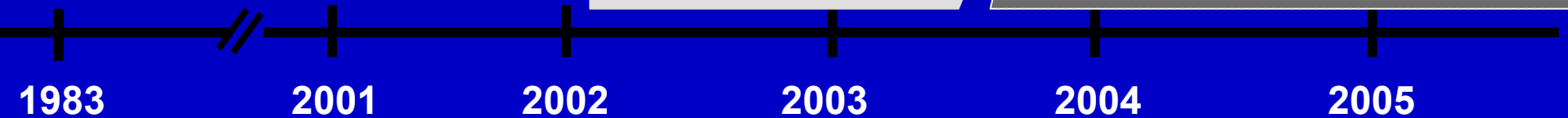
~155 million doses

Dryvax

15 million doses – undiluted
75 million @ 1:5 dilution

**AvP
Vaccine**

70-90 million
doses



Further attenuated vaccines

- **CV178 (Kempe, Galasso)**
- **Modified Vaccinia Ankara**
- **NYVAC**
- **LC18m8 (Japanese strain)**
- **Others (vaccinia as carrier for other antigens)**

Further attenuated vaccines

- Poor replication in skin
- Poor CMI response
- Poor Neut Ab response
- Impossible to do field trial
- No known surrogate end-point
- Pre-vaccinia vaccination

Killed vaccine

- Fair neuts, no CMI
- Transient immune response
- Killed measles vaccine and atypical measles
- Can't do a field trial
- German “result” in 1970's

Major Complications of Smallpox Vaccination

- 1960's studies (Lane, Neff, etc.) done when several vaccination techniques and several NYCBOH vaccines were used.
- No vaccine or technique specific denominators available.

*

Smallpox vaccine Adverse Reaction Rates*

Reaction	Primary Vaccination
Inadvertent inoculation	25-529
Generalized vaccinia	23-242
Eczema vaccinatum	10-39
Progressive vaccinia	0.9-1.5
Post-vaccinial encephalitis	3-12
Death	1

*Rates per million primary vaccinations

Table 1: Smallpox Vaccine Adverse Reaction Rates

(number per million vaccinees) (28)

	NATIONAL SURVEY		TEN-STATE SURVEY	
	All primary (i.e., first-time) vaccinees	Vaccinees >= 1 yr old	All primary (i.e., first-time) vaccinees	Vaccinees >= 1 yr old
Serious, but not life-threatening reactions:				
Inadvertent Inoculation	25.4	27.1	529.2	532.0
Generalized Vaccinia	23.4	17.7	241.5	222.8
Erythema Multiforme	Not Available	Not Available	164.6	131.3
Total number of serious, but not life-threatening reactions:	48.8		935.3	
Life-threatening reactions:				
Postvaccinal Encephalitis/encephalomyelitis	2.9	2.4	12.3	8.6
Progressive Vaccinia (Vaccinia Necrosum)	0.9	1.0	1.5	1.7
Eczema Vaccinatum	10.4	10.6	38.5	41.5
Total number of life-threatening reactions:	14.2		52.3	
Deaths:	1.1	0.6	1.5	None Reported

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