Overview on smallpox vaccines

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Smallpox - features

- Two principle clinical forms of smallpox can be differentiated, which are caused by different strains of Variola virus
  - Variola major: high morbitiy and mortality (case fatality rate of about 30%)
  - Variola minor: milder form with case fatality rate of under 1%
  - Rarely, two fatal disease forms occurred; haemorrhagic and malignant smallpox

- Infected persons are not contagious during the prolonged incubation period (including the initial symptomatic phase with flu-like symptoms, high fever, malaise) of 10-14 days, **virus shedding starts with appearance of rash**

- Postexposure vaccination may prevent from disease and/or death, if given shortly after exposure :
  - Previously unvaccinated: up to 4 days post exposure
  - Previously vaccinated: up to 7 days post exposure

Fenner et al 1988; Mortimer, 2003

Smallpox vaccines

- **First generation vaccines**
  - Manufactured during or at the end of the eradication phase on skin or lymph of animals (e.g calf, sheep).
  - Various vaccinia virus strains were used globally during the eradication phase (e.g. Lister, NYCBH, Tiantan, EM63)
- **Second generation vaccines**
  - Cell culture derived smallpox vaccines employing monoclonal or polyclonal NYCBH or Lister strain vaccines.
- **Third generation vaccines**
  - Highly attenuated smallpox vaccines manufactured by cell culture technology
  - Replication competent – LC16m8
  - Replication deficient – MVA (Imvanex)
- **Other**
  - Oral smallpox vaccines
  - Inactivated vaccines

First generation vaccines

- **Pre-eradication era**
  - Proven field effectiveness by successful eradication of smallpox
  - Major cutaneous reaction ('vaccine take') defined as clinical correlate of protection
  - No common serological correlate has been established
  - Known rare, but serious postvaccinial complications include generalized vaccinia, eczema vaccinatum, progressive vaccinia (vaccinia necrosum), postvaccinial encephalitis and death.
  - These complications occur more frequently in vaccinia-naïve vaccinees than vaccinia-experienced individuals
  - Frequency of occurrence of serious AEFIs depend on vaccine strain used and age of vaccinee

Fenner et al 1988

Estimated frequency of postvaccinial encephalitis (PVE) and death after primary vaccination with different vaccinia virus strains (*Kretzschmar et al. 2006)*

	Expected cases per million vaccinations by vaccinia strain			
	Bern	**Copenhagen**	**Lister**	**NYCBH**
PVE	44.9	33.3	26.2	2.9
Death	55	31.2	8.4	1.4

Estimated frequency of specific AEFIs after primary and re-vaccination with NYCBH strain (*Aragón et al. 2003)*

	Risk of postvaccinial complication per million vaccinations				
	PVE	**Progressive vaccinia**	**Eczema vaccinatum**	**Generalized vaccinia**	**Accidental inoculation**
Primary vaccinee	2.9	1.0	12.8	39.9	64.9
Revaccinee	0.1	0.7	1.0	1.4	16.9

Age related effects (NYCBH)

- Risk of PVE (Risk Ratio 2.8) and generalized vaccinia (Risk Ratio 3.14) highest in children <1 year of age
- Risk of progressive vaccinia highest in adults 20 years and older (Risk Ratio 7.27), but almost all cases occurred in persons with a previously diagnosed hematopoetic malignancy or immunodeficiency condition.

Experience with 1st generation vaccines in the post-eradication era - safety

NCYBH vaccine

In the USA 628,414 subjects of the military and 39,566 first responders and health care workers were vaccinated with Dryvax

- No reports of progressive vaccinia and eczema vaccinatum
- 42 cases of suspect or probable generalized vaccinia, all mild and self-limited
- 97 cases of autoinoculation, all resolved without sequelae
- 2 cases of PVE were reported
- **100 cases of myopericarditis** most likely related to vaccination occurred. Onset of symptoms was coincident with peak viral replication at the vaccination site (at 7-14 days). Increased incidence in primary vaccinees (7.5-fold) compared to background rate among non-vaccinees. No increased incidence in revaccinees.
- Seven cases of dilated cardiomyopathy (DCM) were reported 5-40 weeks after vaccination in previously healthy individuals. Currently no information on background incidence rates is available, but there is a possible link to infection and autoimmune processes.

Neff et al 2008, Poland et al 2005

Experience with 1st generation vaccines in the post-eradication era - safety

Lister vaccine

Vaccination campaign conducted by the Israel Defense Force in recruits 18 years and older in 1991 to 1996. The majority of recruits were revaccinated and ~20% received primary vaccinations.

- Overall, postvaccinial complication rate was 0.4 per 10,000 vaccinations.
- No cases of PVE, progressive vaccinia or death were reported.
- Other serious AEFIs were recorded with the following frequencies:
  - Eczema vaccinatum: 0.15 per 10,000 vaccinations
  - Generalized vaccinia: 0.09 per 10,000 vaccinations
  - Inadvertent inoculation: 0.06 per 10,000 vaccinations
  - Secondary infection: 0.06 per 10,000 vaccinations
  - Erythema multiforme: 0.03 per 10,000 vaccinations

Haim 2000

Second generation vaccines

Produced by cell culture techniques, reduced risk of contamination with adventitious agents

- CJ-50300:
  - polyclonal vaccine derived from NYCBH
  - propagated in serum-free MRC-5 cells
- Elstree vaccines (Elstree-BN, VV Lister/CEP, Elstree/RIVM):
  - polyclonal vaccine virus strains
  - propagated on primary chicken embryo cells or primary rabbit kidney cells

Only very limited information available, but no significant different efficacy and/or safety profile anticipated for 2nd generation smallpox vaccines because of the change in the manufacturing system except of a reduced risk of bacterial infections

- **ACAM2000 (licensed by FDA in 2007):**
  - monoclonal, plaque purified vaccine virus strain derived from NYCBH,
  - animal data suggest reduced pathogenicity compared to polyclonal vaccine strain
  - prepared on MRC-5 cells

Monoclonal 2nd generation vaccine - ACAM2000

Efficacy/immunogenicity evaluated in noninferiority studies using first generation smallpox vaccine Dryvax as comparator

•Vaccinia-naïve subjects: vaccine take rates were non-inferior for ACAM2000 and Dryvax, but GMTs were inferior

•Vaccinia-experienced subjects: vaccine take rates for ACAM2000 were inferior to Dryvax, but GMTs were non-inferior

Safety data based on a total of 2983 subjects, including 1819 revaccinees

•No generalized vaccinia, ocular vaccinia, PVE, progressive vaccinia, erythema multiforme, or eczema vaccinatum

•Most commonly reported AEFI was myopericarditis,

- All cases observed in primary vaccinees, none in revaccinees
- No significant difference in frequency between ACAM2000 and Dryvax
- Incidence of myopericarditis was higher than previously observed in the DoD/DHHS program

•Occurrence of common adverse events was comparable between the two vaccination groups, but generally they were observed at a lower frequency in ACAM2000 recipients than in Dryvax recipients.

ACAM2000 briefing document, FDA 2003
ACAM2000 prescribing information, approved by FDA 2007

Replication competent 3rd generation vaccines – LC16m8

LC16m8 derived from vaccine strain Lister by multiple passages in cell culture at 30°C

–reduced neurovirulence in rabbits and monkeys after i.c. inoculation compared to the parent Lister strain

–replication competent, but one-base deletion of B5R gene results in a truncated B5R protein

–B5R is necessary for efficient formation of extracellular enveloped virus (EEV) particles, which are responsible for dissemination within the host

–B5R is related to complement activation family and major target of neutralising antibodies

Results from animal studies

•Studies using various animal models (mice, rabbits, monkeys) indicate comparable protective vaccine efficacy of LC16m8 compared to Lister or Dryvax vaccine

•Studies in immunocompromised SCID mice indicate that LC16m8 is well tolerated with no serious side effects. Immunization with high doses of LC16m8 did not induce mortality in contrast to Dryvax.

Morikawa 2005, Saijo et al 2006, Empig et al 2006, Meseda et al 2009, Gordon et al 2011

LC16m8 – pre-eradication phase

LC16m8 was evaluated in appr. 10,000 children 0-5 years of age in field studies in 1973-1974; data compared with results from previously performed field studies using the Lister strain vaccine

- Efficacy: Comparable take rates observed for LC16m8 (95.1%) and Lister strain (93.7%), however field effectiveness against smallpox was never demonstrated
- Safety: (8544 subjects closely followed-up)
  - No case of PVE, 8 cases of generalized vaccinia, 1 case of eczema vaccinatum, 9 cases of autoinoculation, 3 cases of convulsions
  - Lower number of subjects with temporary anomalies by electroencephalogram (EEG) in LC16m8 (0/56) than Lister (6/37) vaccine recipients
  - Lower fever rates (7.7% vs 26.6%) and lower local induration at the vaccination site (6.1mm vs 15.3mm) than parental Lister strain

Following licensure over 90,000 doses of vaccine distributed, with no reports of serious AEFIs

Hashizume et al 1985

LC16m8 – recent data

Safety results of clinical trials in humans (~3400 subjects)

•No serious AEFIs and no cases of generalized vaccinia, progressive vaccinia, eczema vaccinatum, or myo-and pericarditis.

•In general the frequency of AEFIs was low (13.9%) with a significantly higher frequency of AEFIs in primary vaccinees than revaccinees.

•The most frequently reported AEFIs were swelling of axillary lymph nodes and low grade fever.

Efficacy/Immunogenicity results from clinical trials

•Vaccinia-naïve subjects: vaccine take rates of 94.4-100%,

•Vaccinia-experienced subjects: vaccine take rates of 86.6%

•90.2% of primary vaccinees had 4-fold increase in neutralising antibody responses

•Antibody responses to specific proteins indicate that LC16m8 induces antibodies against a variety of intracellular mature virus (IMV) proteins as well as against certain extracellular enveloped virus (EEV) proteins (i.e. against A56, but not B5)

Saito et al 2009; Johnson et al 2011; Kennedy et al 2011

Replication deficient 3rd generation vaccines - MVA vaccines

- MVA strains derive from the vaccine strain Ankara by over 570 passages in chick embryo cells (CEC)
- Six major deletions resulting in loss of appr. 30kb of the genome
- Limited ability to replicate in humans and other mammals
- Block in virus morphogenesis, no production of infectious intracellular mature virus (IMV) and extracellular enveloped virus (EEV) particles
- At the end of the pre-eradication era MVA vaccine ($1x10^6$ IU/dose) was given as priming dose prior administration of a traditional smallpox vaccine
- Recently, several MVA vaccines were developed, but they are distinct as they originate from different MVA parental strains
  - **Imvanex** (Imvamune or MVA/BN): monoclonal vaccine strain derived from the 584th passage after serial plaque purification rounds
  - **ACAM3000:** polyclonal vaccine
  - **TBC MVA**: polyclonal vaccine

Mayr et al 1978; Suter et al 2009; Imvanex EPAR 2013

Imvanex (MVA-BN)

Animal data

- Imvanex was tested in various animal models (mouse, rabbit, monkeys)
- Protective efficacy of Imvanex against death was demonstrated following a 2-dose vaccine regimen
- However, in macaques vaccinated twice with Imvanex, there was incomplete suppression of challenge virus replication following lethal aerosolised challenge with monkeypox virus (MPXV) strain Zaire79. In contrast ACAM2000 achieved complete virus suppression.
- Statistically significant correlations were found between dose of Imvanex and probability of survival, but there were animals that did not survive lethal challenge despite seroconversion and animals that survived who had not seroconverted

Samuelsson et al 2008; Garza et al 2009; Stittelaar et al 2005; Hatch et al 2013; Imvanex EPAR 2013

Imvanex (MVA-BN)

Human data

•Several dose-finding studies evaluated the immunogenicity of different vaccination regimens of Imvanex including a booster vaccination with a single dose of traditional smallpox vaccine (Dryvax).

•Clinical take rates were low in vaccination groups having received either 2 doses of $5x10^7$ TCID50 (53.8%) or 2 doses of $1x10^8$ TCID50 intramuscularly (66.7%) prior to Dryvax administration

•Evaluation of sera in a Variola PRNT revealed that the ability to neutralize Variola virus elicited by the MVA regimens is as robust as that elicited by Dryvax alone

•Accelerated vaccination scheme of 2 doses at day 0 and 7 is unfavourable compared to a regular scheme of 2 doses given 4 weeks apart due to higher antibody titers and response rates

•Vaccination regimen of 2 doses of $1x10^8$ TCID50 given 4 weeks apart by s.c. and i.m. administration evaluated in vaccinia naïve and experienced healthy subjects, subjects with history of atopic dermatitis (AD) and HIV infected patients

Frey et al 2007; Damon et al., 2009, Hughes et al 2012; Imvanex EPAR 2013; Vollmar et al 2006

Imvanex (MVA-BN) - Immunogenicity

SCR observed in vaccinia-naïve subjects as measured by PRNT

SCR - PRNT			at Day 7 or 14	Day 28	Day 42
Study	**Health status**	**n**	**SCR % (95%-CI)**	**SCR % (95%-CI)**	**SCR % (95%-CI)**
POX-MVA-005	Healthy	183	45.1 (37.7; 52.6)	56.7 49.1; 64.0)	89.2 (83.7; 93.4)
POX-MVA-008	Healthy	194	5.4 (2.6; 9.8)	24.5 (18.6; 31.2)	86.6 (81.0; 91.1)
	AD	257	5.6 (3.1; 9.3)	26.8 (21.4; 32.7)	90.3 (86.0; 93.6)
POX-MVA-009	Healthy	66	12.1 (5.4; 22.5)	10.6 (4.4; 20.6)	82.5 (70.9; 90.9)
POX-MVA-011	Healthy	88	11.1 (5.2; 20.0)	20.9 (12.9; 31.0)	77.2 (66.4; 85.9)
	HIV	351	15.7 (11.9; 20.1)	22.5 (18.1; 27.4)	60.3 (54.7; 65.8)

SCR observed in vaccinia-experienced subjects as measured by PRNT

SCR - PRNT			At Day 7 or 14	Day 28	Day 42
Study	**Health status**	**n**	**SCR % (95%-CI)**	**SCR % (95%-CI)**	**SCR % (95%-CI)**
POX-MVA-005	Healthy	200	78.5 (72.2; 84.0)	69.8 (63.0; 76.1)	NA
POX-MVA-024	Healthy	61	73.8 (60.9; 84.2)	71.2 (57.9; 82.2)	NA
POX-MVA-011	Healthy	9	75.0 (34.9; 96.8)	62.5 (24.5; 91.5)	85.7 (42.1; 99.6)
	HIV	131	46.0 (37.0; 55.1)	59.7 (50.5; 68.4)	75.6 (67.0; 82.9)

von Krempelhuber et al 2010; Greenberg et al 2013; Imvanex EPAR 2013

Imvanex (MVA-BN) - Safety

Safety data available from 1547 vaccinia-naïve and 534 previously vaccinated subjects

- Most frequently reported AEFIs were injection site reactions and mild to moderate systemic symptoms such as headache, myalgia, nausea. They typically resolved within one week.
- In general, occurrence and frequency of AEFIs were comparable in primary vaccinees and revaccinees.
- In subjects with atopic dermatitis (AD) erythema and swelling at the injection site as well as headache, myalgia, nausea and fatique were more frequently observed than in healthy subjects.
- Worsening of atopic dermatitis was observed in 7% of AD subjects
- 4 serious AEFIs observed, (grade 3 extraocular muscle paresis, pneumonia in a HIV patient, cardiomyopathy, sarcoidosis)
- No case of known postvaccinial complication or myopericarditis

Further confirmatory phase III studies are ongoing and the results are expected to become available in 2016/2017

Imvanex EPAR 2013

Conclusions

First generation vaccines:

- Freeze-dried vaccines; 1 dose administered by scarification
- Proven effectiveness against smallpox in pre- and postexposure settings
- High risk of rare but serious AEFIs

Second generation vaccines (incl. ACAM2000):

- Freeze-dried vaccines; 1 dose administered by scarification
- Based on same virus strains as 1st generation vaccines
- High likelihood that same effectiveness in pre- and postexposure settings and comparable safety profile as 1st generation vaccines

Replication-competent vaccine LC16m8:

- Freeze-dried vaccine; 1 dose administered by scarification
- No proven field effectiveness; efficacy comparable to 1st and 2nd generation vaccines
- High likelihood that comparable effectiveness in pre- and postexposure settings
- Safety data from over 100,000 immunocompetent subjects suggest low risk of serious AEFIs

Replication-deficient vaccine – Imvanex (MVA-BN)

- Liquid vaccine; 2 doses given subcutaneously 4 weeks apart
- No proven field effectiveness; SCR of ~80-90% in healthy and AD subjects
- Limited safety data from about 2100 subjects including HIV and AD patients; data suggest low risk of serious AEFIs specifically in high risk groups