2013 WHO smallpox consultation

Disclaimer: These GRADE tables are based on the systematic literature research on smallpox vaccines that was conducted to inform the 2013 WHO smallpox consultation. The tables were developed by the WHO SAGE secretariat and have not been endorsed by the members of the smallpox consultation.

Smallpox vaccines used during the eradication

Table 1: Clinical protection of vaccines used during the eradication

Population : Immunocompetent individuals
Intervention: Vaccine developed before eradication produced with NYCBH or Lister strain (propagated and harvested primarily from skin of live animals, 10^8 pock/ml, administrated with bifurcated needles)
Comparison: No vaccination
Outcome : Cases of vaccinia

PICO Question: What is the scientific evidence of the clinical protection against smallpox disease of any dose of vaccine used during or after eradication in immunocompetent individuals produced with NYCBH or Lister strain compared to no vaccination?				
			Rating	Adjustment to rating
Quality Assessment	No of studies/starting rating		7 observational[1]	2
	Factors decreasing confidence	Limitation in study design	None serious	0
		Inconsistency	None serious	0
		Indirectness	None serious[2]	0
		Imprecision	None serious	0
		Publication bias	None detected	0
	Factors increasing confidence	Strength of association/ large effect	Applicable[3]	+2
		Dose-response	Not applicable	0
		Antagonistic /mitigated bias and confounding	Not applicable	0
	Final numerical rating of quality of evidence			**4**
Summary of Findings	**Statement on quality of evidence**			We are very confident that the true effect lies close to that of the estimate of effect on health outcome
	Conclusion			No randomized controlled trials have been used to assess efficacy, yet large observational studies and global eradication of smallpox in 1980 indicate that the vaccine is highly effective.

[1] Smallpox vaccines used during eradication produced with NYCBH or Lister strain were evaluated for clinical protection in the pre- and post-eradication phase. Secondary attack rate among household contacts suggests vaccine effectiveness to be 90.7-97.1% (Fenner et al. 1988). Major cutaneous reaction (vaccine take) was 61% in previously vaccinated (Orr et al. 2004), 95.6% (Bossi et al. 2008), 97.2% (Frey et al.2002), 99% (Auckland et al. 2005), 100% (Hsieh et al. 2006, Kim et al. 2005) respectively. It was shown that pre-existing antibodies against vaccinia inversely correlated with the rates of clinical take.

[2] Vaccine-related major cutaneous reaction was recognized as clinical correlate of protection, hence no downgrading for indirectness.

[3] Strong evidence of high vaccine effectiveness.

Reference List

(1) Auckland C, Cowlishaw A, Morgan D, Miller E. Reactions to small pox vaccine in naive and previously-vaccinated individuals. Vaccine 2005 Jul 14;23(32):4185-7.

(2) Bossi P, Gay F, Fouzai I, Combadiere B, Brousse G, Lebrun-Vignes B, et al. Demographic and clinical factors associated with response to smallpox vaccine in preimmunized volunteers 2. PLoS One 2008;3(12):e4087.

(3) Frey SE, Couch RB, Tacket CO, Treanor JJ, Wolff M, Newman FK, et al. Clinical responses to undiluted and diluted smallpox vaccine. N Engl J Med 2002 Apr 25;346(17):1265-74.

(4) Hsieh SM, Chen SY, Sheu GC, Hung MN, Chou WH, Chang SC, et al. Clinical and immunological responses to undiluted and diluted smallpox vaccine with vaccinia virus of Lister strain. Vaccine 2006 Jan 23;24(4):510-5.

(5) Kim SH, Yeo SG, Jang HC, Park WB, Lee CS, Lee KD, et al. Clinical responses to smallpox vaccine in vaccinia-naive and previously vaccinated populations: undiluted and diluted Lancy-Vaxina vaccine in a single-blind, randomized, prospective trial. J Infect Dis 2005 Sep 15;192(6):1066-70.

(6) Orr N, Forman M, Marcus H, Lustig S, Paran N, Grotto I, et al. Clinical and immune responses after revaccination of israeli adults with the Lister strain of vaccinia virus. J Infect Dis 2004 Oct 1;190(7):1295-302.

(7) Fenner F, Henderson DA, Arita I, Jezek Z, Ladnyi ID (1988). Smallpox and its eradication. Geneva: World Health Organisation.

Smallpox vaccines used during the eradication

Table 2: Safety of first generation of smallpox vaccines used during the eradication

Population : Immunocompetent individuals
Intervention: Vaccine developed before eradication produced with NYCBH or Lister strain (propagated and harvested primarily from skin of live animals, 10^8 pock/ml, administrated with bifurcated needles)
Comparison: No vaccination
Outcome : Cases of vaccinia

PICO Question: In immunocompetent individuals, what is the incidence of serious adverse events for any dose of vaccine used during eradication produced with NYCBH or Lister strain compared to no vaccination?				
			Rating	Adjustment to rating
Quality Assessment	No of studies/starting rating		10 observational[4]	2
	Factors decreasing confidence	Limitation in study design	None serious	0
		Inconsistency	None serious	0
		Indirectness	None serious	0
		Imprecision	None serious	0
		Publication bias	None detected	0
	Factors increasing confidence	Strength of association/ large effect	Not applicable	0
		Dose-response	Not applicable	0
		Antagonistic /mitigated bias and confounding	Applicable[5]	+1
	Final numerical rating of quality of evidence			**3**
Summary of Findings	**Statement on quality of evidence**			We are moderately confident in the estimate of effect on health outcome. The true effect is likely to be close to the estimate of the effect
	Conclusion			Reports of serious adverse events following the use of first generation smallpox vaccines were assessed during the pre-and post-eradication era. Risk of serious adverse events such as postvaccinal encephalitis, myopericarditis and death were dependent on strain ,age range and

[4] Smallpox vaccines used during eradication produced with NYCBH or Lister strain were evaluated for safety in the pre- and post-eradication phase. Serious adverse events reported were generalized vaccinia, eczema vaccinatum, progressive vaccinia, postvaccinal encephalitis and death. Fenner et al. 1988, Aragon et al. 2003 and Kretzschmar et al. 2006 found in the pre-eradication era, risk was dependent on strain and age of vaccinee. The highest risk of postvaccinal encephalitis and death rate was reported after the use of vaccine made from the Bern strain (44.9 and 55 per 1.000.000 vaccines) (Kretzschmar et al. 2006). Revaccinees had a significantly lower risk of severe adverse events. Orr et al.2004, Haim et al.2000, Hsieh et al.2006, Kim et al. 2005, Auckland et al. 2005 and Bossi et al. 2008, evaluated the safety of the vaccine in the post-eradication era. Overall postvaccination complication rate was 40/1.000.000 vaccines (Haim et al. 2000) Myopericarditis incidence was 160/1.000.000 after primary vaccination, 7.5-folder higher than in non-vaccinated background rate (Poland et al, 2005).

[5] Upgraded for consistency of findings between studies, across different settings, different investigators and different designs.

		first-time or re-vaccination

Reference List

(1) Aragon TJ, Ulrich S, Fernyak S, Rutherford GW. Risks of serious complications and death from smallpox vaccination: a systematic review of the United States experience, 1963-1968. BMC Public Health 2003 Aug 11;3:26.

(2) Auckland C, Cowlishaw A, Morgan D, Miller E. Reactions to smallpox vaccine in naive and previously-vaccinated individuals. Vaccine 2005 Jul 14;23(32):4185-7.

(3) Bossi P, Gay F, Fouzai I, Combadiere B, Brousse G, Lebrun-Vignes B, et al. Demographic and clinical factors associated with response to smallpox vaccine in preimmunized volunteers 2. PLoS One 2008;3(12):e4087.

(4) Haim M, Gdalevich M, Mimouni D, Ashkenazi I, Shemer J. Adverse reactions to smallpox vaccine: the Israel Defense Force experience, 1991 to 1996. A comparison with previous surveys. Mil Med 2000 Apr;165(4):287-9.

(5) Hsieh SM, Chen SY, Sheu GC, Hung MN, Chou WH, Chang SC, et al. Clinical and immunological responses to undiluted and diluted smallpox vaccine with vaccinia virus of Lister strain. Vaccine 2006 Jan 23;24(4):510-5.

(6) Kim SH, Yeo SG, Jang HC, Park WB, Lee CS, Lee KD, et al. Clinical responses to smallpox vaccine in vaccinia-naive and previously vaccinated populations: undiluted and diluted Lancy-Vaxina vaccine in a single-blind, randomized, prospective trial. J Infect Dis 2005 Sep 15;192(6):1066-70.

(7) Kretzschmar M, Wallinga J, Teunis P, Xing S, Mikolajczyk R. Frequency of adverse events after vaccination with different vaccinia strains. PLoS Med 2006 Aug;3(8):e272.

(8) Neff J, Modlin J, Birkhead GS, Poland G, Robertson RM, Sepkowitz K, et al. Monitoring the safety of a smallpox vaccination program in the United States: report of the joint Smallpox Vaccine Safety Working Group of the advisory committee on immunization practices and the Armed Forces Epidemiological Board. Clin Infect Dis 2008 Mar 15;46 Suppl 3:S258-S270.

(9) Orr N, Forman M, Marcus H, Lustig S, Paran N, Grotto I, et al. Clinical and immune responses after revaccination of israeli adults with the Lister strain of vaccinia virus. J Infect Dis 2004 Oct 1;190(7):1295-302.

(10) Poland GA, Grabenstein JD, Neff JM. The US smallpox vaccination program: a review of a large modern era smallpox vaccination implementation program. Vaccine 2005 Mar 18;23(17-18):2078-81.

Smallpox ACAM-2000 vaccines

Table 3: Clinical protection of vaccines used during the eradication

Population : Immunocompetent individuals
Intervention: ACAM-2000 vaccine
Comparison: No vaccination
Outcome : Cases of vaccinia

PICO Question: What is the scientific evidence of the clinical protection of any dose of ACAM-2000 vaccine against smallpox disease in immunocompetent individuals compared to no vaccination?				
			Rating	Adjustment to rating
Quality Assessment	No of studies/starting rating		5 RCT/1observational[6]	4
	Factors decreasing confidence	Limitation in study design	Serious[7]	-1
		Inconsistency	None serious	0
		Indirectness	None serious[8]	0
		Imprecision	None serious	0
		Publication bias	None detected	0
	Factors increasing confidence	Strength of association/ large effect	Applicable[9]	(+2)
		Dose-response	Not applicable	0
		Antagonistic /mitigated bias and confounding	Not applicable	0
	Final numerical rating of quality of evidence			**4**
Summary of Findings	**Statement on quality of evidence**			We are very confident that the true effect lies close to that of the estimate of effect on the health outcome.
	Conclusion			ACAM-2000 suggests dose-dependent levels of clinical protection of 27%-100% in previously vaccinated and unvaccinated participants.

[6] 6 Clinical studies, with a total of 2983 participants, evaluated safety and/or efficacy of ACAM-2000. Except one (H-400-008) all studies were randomized, controlled trials. Two Phase 1 studies, conducted in vaccinia-naive participants, suggest 99% and 100% efficacy. Two Phase 2 studies suggest dose-dependent efficacy of 59%-100% in vaccinia-naive participants and dose-dependent efficacy of 27%-88% in previously vaccinated participants. Two Phase 3 trials suggest 96% efficacy in vaccinia-naive and 84% in previously vaccinated participants.

[7] No study reported detailed information on allocation concealment.

[8] Vaccine-related major cutaneous reaction (vaccine take) was recognized as clinical correlate of protection, hence no downgrading for indirectness.

[9] Strong evidence of high vaccine effectiveness.

Reference List (1-3)

(1) Nalca A, Zumbrun EE. ACAM2000: the new smallpox vaccine for United States Strategic National Stockpile. Drug Des Devel Ther 2010;4:71-9.

(2) Monath TP, Caldwell JR, Mundt W, Fusco J, Johnson CS, Buller M, et al. ACAM2000 clonal Vero cell culture vaccinia virus (New York City Board of Health strain)--a second-generation smallpox vaccine for biological defense. Int J Infect Dis 2004 Oct;8 Suppl 2:S31-S44.

(3) Acambis I. FDA C. ACAM2000™ smallpox vaccine: Vaccines and Related Biological Products Advisory Committee (VRBPAC) 2007. 2013.

Smallpox ACAM-2000 vaccine

Table 4: Safety of ACAM-2000 smallpox vaccines

Population : Immunocompetent individuals
Intervention: ACAM-2000 vaccine
Comparison: No vaccination
Outcome : Serious adverse events

PICO Question: In immunocompetent individuals, what is the incidence of serious adverse events for any dose of ACAM-2000 vaccine compared to no vaccination?				
			Rating	Adjustment to rating
Quality Assessment	No of studies/starting rating		5 RCT/ 1 observational[10]	4
	Factors decreasing confidence	Limitation in study design	Serious[11]	-1
		Inconsistency	None serious	0
		Indirectness	None serious	0
		Imprecision	Serious[12]	-1
		Publication bias	None detected	0
	Factors increasing confidence	Strength of association/ large effect	Not applicable	0
		Dose-response	Not applicable	0
		Antagonistic /mitigated bias and confounding	Not applicable	0
	Final numerical rating of quality of evidence			**2**
Summary of Findings	**Statement on quality of evidence**			Our confidence in the estimate of the effect on the health outcome is limited
	Conclusion			Reports of severe adverse events following the use of ACAM-2000 smallpox vaccine were assessed in 6 clinical trials including 2983 participants. No cases of severe adverse events or death were reported except 7 cases of myocarditis, all in previously unvaccinated participants.

[10] 6 Clinical trials, with a total of 2983 participants, evaluated the safety of ACAM-2000. Except one all studies were randomized, controlled trials. No cases of generalized vaccinia, ocular vaccinia, postvaccinial encephalitis, progressive vaccinia, erythema multiforme, or pvE were reported with ACAM2000. However, 7 (5.73 events per thousand vaccinations) cases of suspect or probable myocarditis in subjects treated with ACAM2000 were identified. All subjects who experienced myocarditis were previously naïve to vaccinia; no cases were detected in previously vaccinated subjects. One of the 7 subjects was hospitalized while the others were sub-clinical and received no treatment. One participant experienced a single new onset seizure (Monath et al 2004).

[11] No study reported detailed information on allocation concealment.

[12] Number of study participants possibly too small to detect rare serious adverse events.

Reference List(1-3)

(1) Nalca A, Zumbrun EE. ACAM2000: the new smallpox vaccine for United States Strategic National Stockpile. Drug Des Devel Ther 2010;4:71-9.

(2) Monath TP, Caldwell JR, Mundt W, Fusco J, Johnson CS, Buller M, et al. ACAM2000 clonal Vero cell culture vaccinia virus (New York City Board of Health strain)--a second-generation smallpox vaccine for biological defense. Int J Infect Dis 2004 Oct;8 Suppl 2:S31-S44.

(3) Acambis I. FDA C. ACAM2000™ smallpox vaccine: Vaccines and Related Biological Products Advisory Committee (VRBPAC) 2007. 2013.

LC16m8 smallpox vaccine

Table 5: Clinical protection of LC16m8 smallpox vaccine

Population : Immunocompetent individuals
Intervention: LC16m8 vaccine
Comparison: No vaccination
Outcome : Cases of vaccinia

PICO Question: What is the scientific evidence of the clinical protection of any dose of LC16m8 vaccine against smallpox disease in immunocompetent individuals compared to no vaccination?				
			Rating	Adjustment to rating
Quality Assessment	No of studies/starting rating		1/RCT 2/ observational[13]	4
	Factors decreasing confidence	Limitation in study design	None serious	0
		Inconsistency	None serious	0
		Indirectness	None serious[14]	0
		Imprecision	None serious	0
		Publication bias	None detected	0
	Factors increasing confidence	Strength of association/ large effect	Applicable[15]	(+1)
		Dose-response	Not applicable	0
		Antagonistic /mitigated bias and confounding	Not applicable	0
	Final numerical rating of quality of evidence			**4**
Summary of Findings	**Statement on quality of evidence**			We are very confident that the true effect lies close to that of the estimate of effect on health outcome
	Conclusion			LC16m8 was administered in pre- and post-eradication, yet has not been used in endemic settings, hence has not proven effectiveness in field settings. Efficacy is high, ranging from 94.4% -100% in vaccinia-naive and 86% in previously vaccinated individuals.

[13] In the pre-eradication phase, LC16m8 was administered to 10,578 children 0-5 years of age. Vaccine take rate was 95.1% (Fenner et al. 1988, Hashizume S et al 1985). Post-eradication, one RCT (Kennedy et al. 2011) demonstrated efficacy (vaccine take) in vaccinia-naive participants of 100% (n=125). The overall proportion of clinical take was significantly higher in primary vaccinees (1443/1529 [94.4%; 95% confidence interval {CI}, 93.2%-95.9%]) than in revaccinees (1465/1692 [86.6%; 95% CI, 85.0%-88.2%]) (P<.001) (Saito et al.2009)

[14] Vaccine-related major cutaneous reaction (vaccine take) was recognized as clinical correlate of protection, hence no downgrading for indirectness.

[15] Strong evidence of high vaccine effectiveness.

Reference List(1-3)

(1) Fenner F, Henderson DA, Arita I, Jezek Z, Ladnyi ID (1988). Smallpox and its eradication. Geneva: World Health Organisation. 2013.

(2) Hashizume S, Yoshizawa N, Morita M, Suzuki K. Properties of attenuated mutant of vaccinia virus, LC16m8, derived from Lister strain. In: Quinnan ed, Vaccinia viruses as vectors for vaccine antigens. Elsevier; 1985. p87ff

(2) Kennedy JS, Gurwith M, Dekker CL, Frey SE, Edwards KM, Kenner J, et al. Safety and immunogenicity of LC16m8, an attenuated smallpox vaccine in vaccinia-naive adults 2. J Infect Dis 2011 Nov;204(9):1395-402.

(3) Saito T, Fujii T, Kanatani Y, Saijo M, Morikawa S, Yokote H, et al. Clinical and immunological response to attenuated tissue-cultured smallpox vaccine LC16m8 1. JAMA 2009 Mar 11;301(10):1025-33.

LC16m8 smallpox vaccine

Table 6: Safety of LC16m8 smallpox vaccine

Population : Immunocompetent individuals
Intervention: LC16m8 vaccine (any dose)
Comparison: No vaccination
Outcome : Serious adverse events

PICO Question: In immunocompetent individuals, what is the incidence of serious adverse events for any dose of LC16m8 vaccine compared to no vaccination?				
			Rating	Adjustment to rating
Quality Assessment	No of studies/starting rating		1 RCT/ 3observational[16]	4
	Factors decreasing confidence	Limitation in study design	None serious	0
		Inconsistency	None serious	0
		Indirectness	None serious	0
		Imprecision	Serious[17]	-1
		Publication bias	None detected	0
	Factors increasing confidence	Strength of association/ large effect	Not applicable	0
		Dose-response	Not applicable	0
		Antagonistic /mitigated bias and confounding	Not applicable	0
	Final numerical rating of quality of evidence			**3**
Summary of Findings	**Statement on quality of evidence**			We are moderately confident in the estimate of effect on health outcome. The true effect is likely to be close to the estimate of the effect
	Conclusion			Reports of serious adverse events following the use of LC16m8 vaccines were reported during the pre-eradication era. Post-licensure studies and recent studies report no serious adverse events.

[16] Fenner et al. 1988: Out of 8,544 vaccinees, one case of eczema vaccinatum, 3 cases of convulsions, 8 cases of general vaccinia were noted. More than 90.000 doses were distributed in Japan after licensure in 1975 and no reports on serious adverse events were reported (Hashizume et al.1985). Saito et al. 2009 with 3221 participants, Kennedy et al 2011 with 125 vaccinees observed no serious adverse events.

[17] Number of study participants possibly too small to detect rare serious adverse events.

Reference List(1-4)

(1) Hashizume S, Yoshizawa N, Morita M, Suzuki K. Properties of attenuated mutant of vaccinia virus, LC16m8, derived from Lister strain. In: Quinnan ed, Vaccinia viruses as vectors for vaccine antigens. Elsevier; 1985. p87ff .

(2) Fenner F, Henderson DA, Arita I, Jezek Z, Ladnyi ID (1988). Smallpox and its eradication. Geneva: World Health Organisation. 2013.

(3) Kennedy JS, Gurwith M, Dekker CL, Frey SE, Edwards KM, Kenner J, et al. Safety and immunogenicity of LC16m8, an attenuated smallpox vaccine in vaccinia-naive adults 2. J Infect Dis 2011 Nov;204(9):1395-402.

(4) Saito T, Fujii T, Kanatani Y, Saijo M, Morikawa S, Yokote H, et al. Clinical and immunological response to attenuated tissue-cultured smallpox vaccine LC16m8 1. JAMA 2009 Mar 11;301(10):1025-33.

MVA smallpox vaccines

Table 7: Clinical protection of MVA smallpox vaccines (Imvanex)

Population : Immunocompetent individuals
Intervention: MVA smallpox vaccines
Comparison: No vaccination
Outcome : Cases of vaccinia

PICO Question: What is the scientific evidence of the clinical protection of any dose of MVA vaccine against smallpox disease in immunocompetent individuals compared to no vaccination?				
			Rating	Adjustment to rating
Quality Assessment	No of studies/starting rating		3 RCT/2 observational	4
	Factors decreasing confidence	Limitation in study design	Serious[18]	-1
		Inconsistency	None serious	0
		Indirectness	Serious[19]	-1
		Imprecision	None serious	0
		Publication bias	None detected	0
	Factors increasing confidence	Strength of association/ large effect	Not applicable	0
		Dose-response	Not applicable	0
		Antagonistic /mitigated bias and confounding	Not applicable	0
	Final numerical rating of quality of evidence			**2**
Summary of Findings	**Statement on quality of evidence**			Our confidence in the estimate of the effect on the health outcome is limited
	Conclusion			MVA vaccine has not demonstrated clinical protection in endemic settings. Neutralizing antibodies are used as correlate of protection.

Reference List (1)

(1) EMA.Imvanex: EPAR - Product Information. http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/002596/WC500147896.pdf, published 16/08/2013, accessed 11.10.2013.

[18] Immunogenicity was evaluated in 5 main clinical studies. One study was partially randomised, one study was partially blinded. The study population (>1000 participants) was over 18 years and male as well as female. Seroconversion rates were 77.2%-89.2% after two doses in vaccinia naive and 77.6%-78.5% after one booster dose in vaccinia experiences subjects.

[19] Neutralizing antibody response was evaluated by plaque reduction neutralization assays after two doses of MVA vaccine in vaccinia-naive and vaccinia experienced individuals. Vaccine has not been used in endemic settings.

MVA smallpox vaccines

Table 8: Safety of MVA smallpox vaccines

Population : Immunocompetent individuals
Intervention: MVA smallpox vaccines
Comparison: No vaccination
Outcome : Serious adverse events

PICO Question: In immunocompetent individuals, what is the incidence of serious adverse events for any dose of MVA vaccine compared to no vaccination?				
			Rating	Adjustment to rating
Quality Assessment	No of studies/starting rating		6 RCT/ 7 observational[20]	4
	Factors decreasing confidence	Limitation in study design	Serious[21]	-1
		Inconsistency	None serious	0
		Indirectness	None serious	0
		Imprecision	Serious[22]	-1
		Publication bias	None detected	0
	Factors increasing confidence	Strength of association/ large effect	Not applicable	0
		Dose-response	Not applicable	0
		Antagonistic /mitigated bias and confounding	Not applicable	0
	Final numerical rating of quality of evidence			**2**
Summary of Findings	**Statement on quality of evidence**			Our confidence in the estimate of the effect on the health outcome is limited
	Conclusion			Reports of serious adverse events following the use of MVA smallpox vaccines were assessed in 14 clinical trials and post-licensure data report a low risk of serious adverse events in immunocompetent individuals following immunization with MVA vaccine.

[20] In total 14 clinical trials with 1547 vaccinia naive and 534 previously vaccinated subjects. 3 RCTs partially or single blinded, one RCT partially randomized. Two serious adverse events possibly linked to immunization were described in immunocompetent individuals: One case of extraocular muscle paresis and one case of sarcoidosis. Postmarketing data from 145.000 individuals from the pre-eradication where MVA (100x lower number of infectious units than current MVA vaccines) was used as priming dose before regular immunization with Lister-Elstree (Stickl et al. 1974; Mayr et al. 1978) identified no serious adverse events.

[21] RCT: Vaccinator unblinded. Total number of study participants might not allow detection of rare serious adverse events.

[22] During the pre-eradication era, MVA with reduced infectious units compared to the current MVA vaccines was used in 145000 individuals as a primer dose. No serious adverse events were detected.

Reference List(1-6)

(1) EMA.Imvanex: EPAR - Product Information. http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/002596/WC500147896.pdf, published 16/08/2013, accessed 11.10.2013. 2013.

(2) Frey SE, Newman FK, Kennedy JS, Sobek V, Ennis FA, Hill H, et al. Clinical and immunologic responses to multiple doses of IMVAMUNE (Modified Vaccinia Ankara) followed by Dryvax challenge 1. Vaccine 2007 Dec 12;25(51):8562-73.

(3) Vollmar J, Arndtz N, Eckl KM, Thomsen T, Petzold B, Mateo L, et al. Safety and immunogenicity of IMVAMUNE, a promising candidate as a third generation smallpox vaccine 1. Vaccine 2006 Mar 15;24(12):2065-70.

(4) von KA, Vollmar J, Pokorny R, Rapp P, Wulff N, Petzold B, et al. A randomized, double-blind, dose-finding Phase II study to evaluate immunogenicity and safety of the third generation smallpox vaccine candidate IMVAMUNE 1. Vaccine 2010 Feb 3;28(5):1209-16.

(5) Stickl H, Hochstein-Mintzel V, Mayr A, Huber HC, Schafer H, Holzner A. [MVA vaccination against smallpox: clinical tests with an attenuated live vaccinia virus strain (MVA) (author's transl)]. Dtsch Med Wochenschr 1974 Nov 22;99(47):2386-92.

(6) Mayr A, Stickl H, Muller HK, Danner K, Singer H. [The smallpox vaccination strain MVA: marker, genetic structure, experience gained with the parenteral vaccination and behavior in organisms with a debilitated defence mechanism (author's transl)]. Zentralbl Bakteriol B 1978 Dec;167(5-6):375-90.