Human Ad5-based FMD vaccines

Teresa de los Santos

Plum Island Animal Disease Center, ARS, USDA, USA

Eu-FMD, Borgo Egnazia -Puglia - Italy
October 29-31, 2018

USDA

Harnessing the power of livestock to drive sustainable development

Sector can make major contributions to the 2030 agenda, but important choices have to be made

A pastoralist in South Sudan coats his animals in ash to protect them from flies. For millions of people around the globe, cattle are the foundation of their livelihoods and way of life.

17 October 2018, Rome - A new FAO report highlights the multiple

FAO news Oct 18, 2018

- **Currently, livestock production employs at least 1.3 B people worldwide**
- **About 600 M of the world's poorest households keep livestock as an essential source of income**
- Between 2000-2014, global production of meat rose by 39 %; milk production increased by 38 %
- Meat production is projected to increase another 19%, and milk production another 33% by 2030
- **Livestock production accounts for 40 % agriculture output in developed countries and 20 % of agricultural output in developing countries**
- **Animals remain an important source of power.** In India, 2/3 of the country's cultivated area is ploughed using animal energy, and 14 M animal-drawn carts haul up to 15 % of the country's total freight.
- Advanced genetics, feeding systems, animal health controls and other technologies over the past four decades allowed industrialized countries to reduce their overall land requirements for livestock by 20 % while doubling meat production.
- **Wider adoption of existing best practices and technologies in feeding, health and husbandry,** and manure management - as well as greater use of improved technologies - could help the global livestock sector **cut its GHG emissions by as much as 30 %**

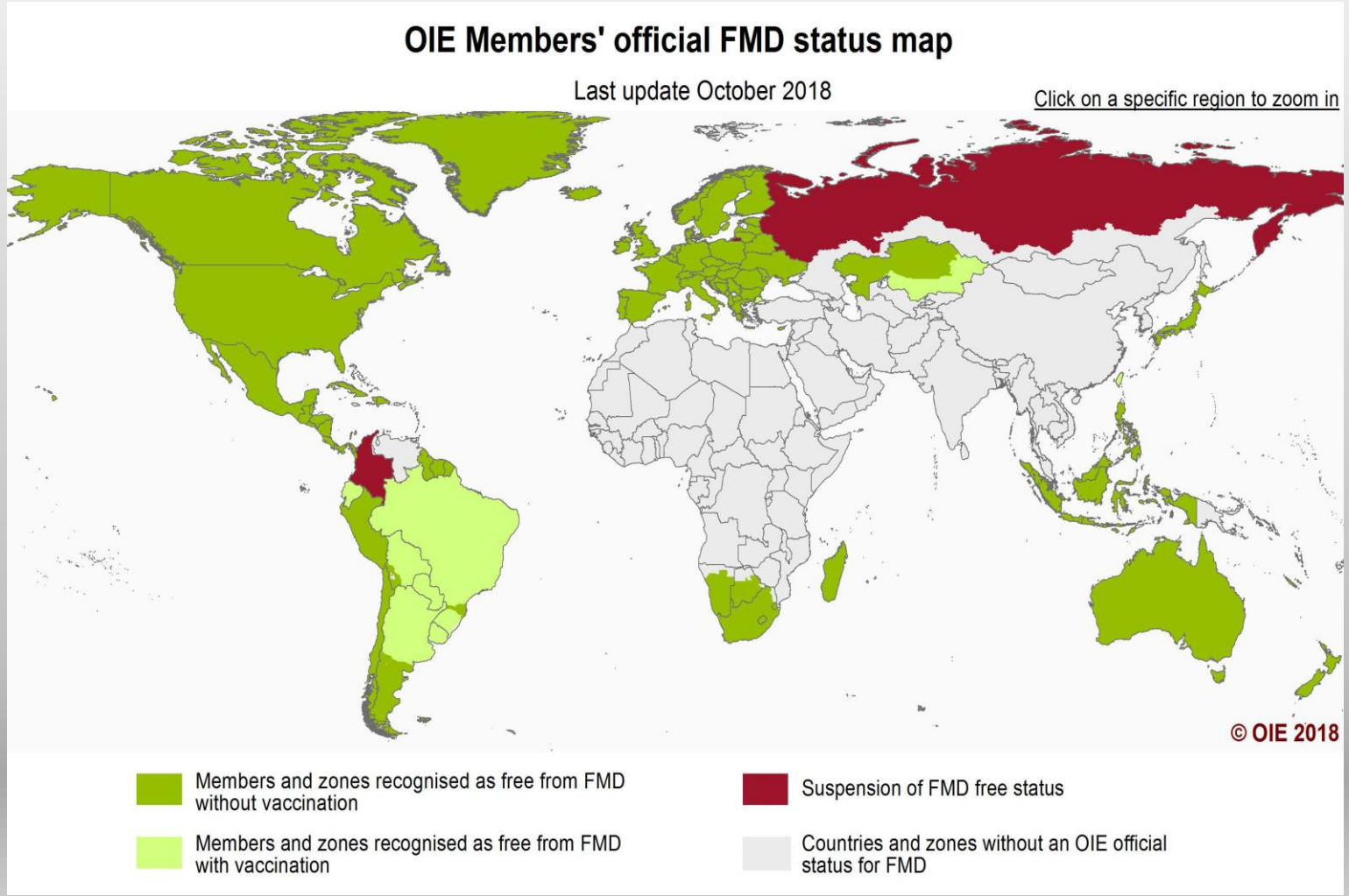
FAO news Oct 18, 2018

FMD: a threat for world development and sustainability

- Taiwan (1997), slaughter 5 M animals. Cost > $ 6B*
- UK, The Netherlands (2001), slaughtered 10 M animals. Cost > $ 14B
- Argentina, Brazil, Uruguay (2000). Paraguay (2011)
- UK (2007). Release of virus from Pirbright vaccine producing facility. Cost > $200 M
- China, Taiwan, S. Korea, Russia (2010-2011). Slaughter more than 3M animals. Cost >$ 2B
- Japan (2010). Slaughter >300,000 animals. Cost > $ 1B

**1.2 % of Taiwan GDPs ($ 489B) ; SA GDP $ 366B*

Most of the inhabited world is endemic for FMD



FMD is endemic in ~ 50 % of Earth, in regions that account for 76 % of the World population

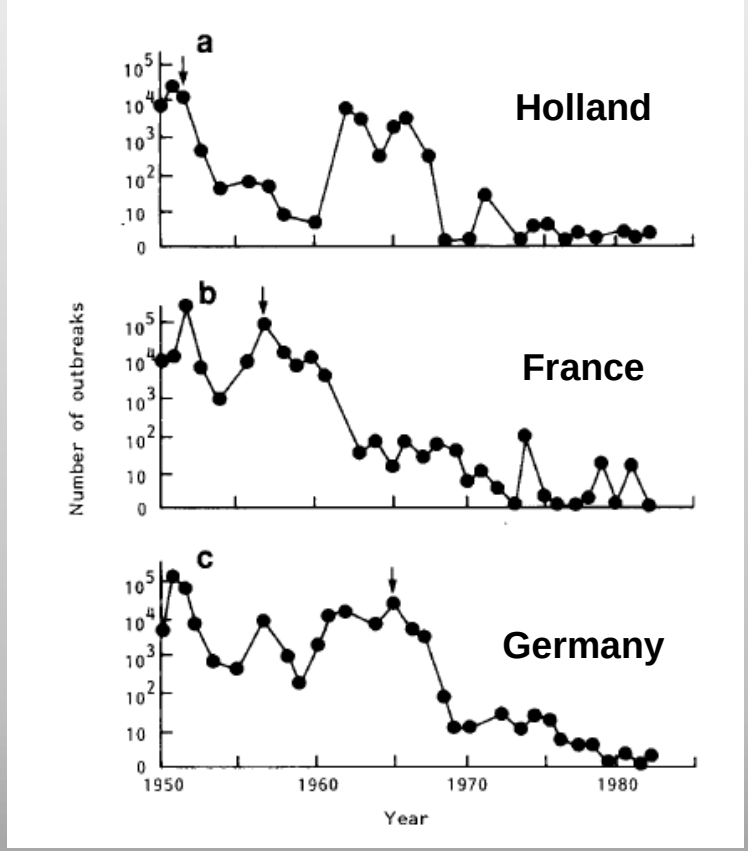
Continent	Area Square meters	Population
Asia	44.4 M	4.44 B
Africa	30.2 M	1.21 B
North America	24.5M	580 M
South America	17.8 M	422 M
Antarctica	14.2 M	1,000-4,000
Europe	10.3 M	738 M
Australia	7.7 M	24 M

74.6 M m^2
5.65 B people

60.3 M m^2
1.77 B people

Methods to Control FMD Outbreaks

- Restrict movement of susceptible animals and their products
- Slaughter infected and susceptible in-contact animals in developed countries (developing countries would not slaughter these animals – allow them to recover)
- Disinfect contaminated areas
- Vaccinate with an inactivated whole virus antigen in formulation with adjuvant
- Inactivated vaccine was a critical component of the strategy that resulted in elimination of FMD from Western Europe in the 1980's and from Uruguay and other South American countries in the 1990's



F. Brown, Vaccine, 10:1022-26,1992

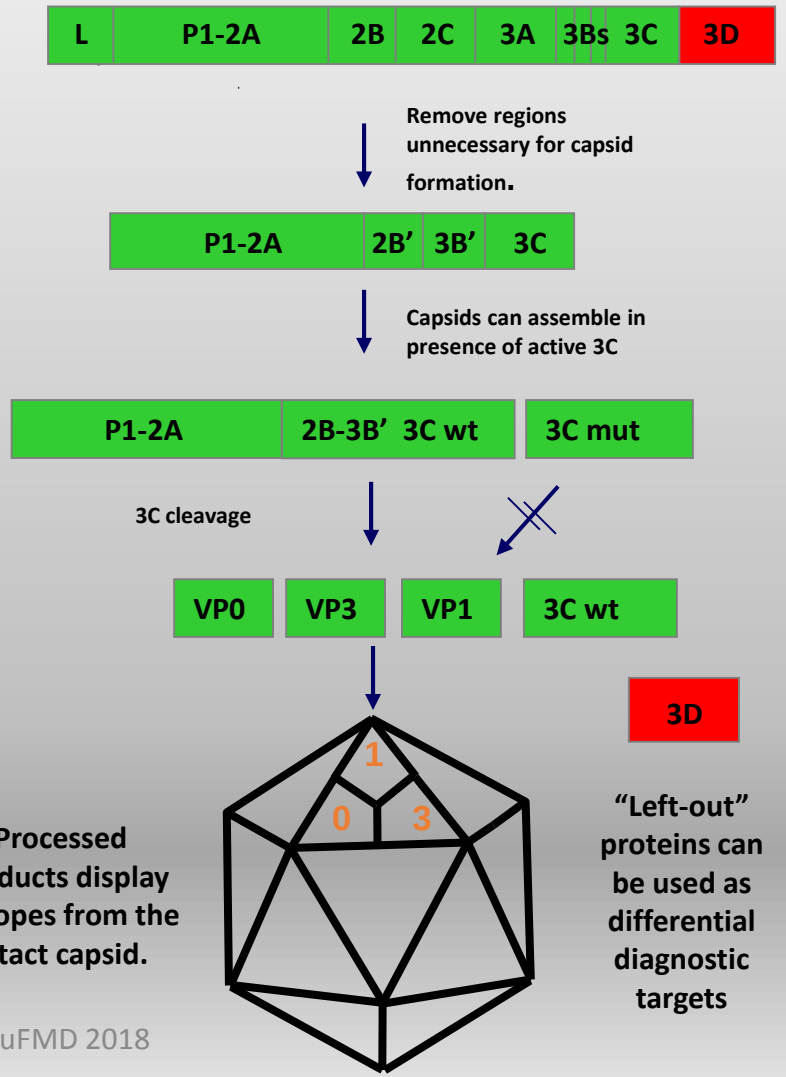
Current inactivated vs ideal vaccine profile

	Characteristics	Current vaccine*	Ideal vaccine
Efficacy:	Protective immunity after one dose	No	Yes
	Onset of protection (days post vaccination)	7-21	1
	Long-lasting immunity (>1 year)	No	Yes
	Cross-protection within serotype	+/-	Yes
	Cross protection across serotypes	No	Yes
	Prevents primary infection	No	Yes
	Prevents carrier state in ruminants	No	Yes
	Efficacious by multiple routes of inoculation	NA	Yes
Safety:	Does not require high containment for manufacturing	No	Yes
	Safe in all target species	Yes	Yes
	Withdrawal for food consumption (days post vaccination)	60	<30
	Genetically stable (unable to revert-to-virulence)	NA	Yes
Other	Development of relevant antigens against emerging viral strains	Months	Days/weeks
	Featured long shelf life (> 2 years)	No	Yes
	Intrinsic negative DIVA markers	No	Yes
	Cost	Moderate	Low
	Thermal stability	No	Yes

Human Ad5-based FMD vaccine: in vivo delivery of VLPs

- Contains all protective epitopes present on current inactivated virus vaccine but lacks infectious viral nucleic acid and non-structural protein (NSP)
- Allows to *"cleanly"* distinguish vaccinated from infected animals using 3D and other 3B NSP diagnostic tests (FMD cassette is missing 3B1 epitope recognized in commercial diagnostics)
- Can be safely produced in the United States (e.g. Antelope Valley Bios, Est. Lic 419)

Mayr et al, 1999, 2001



Ad5-FMD Vaccine (A24) in effective in swine and cattle

ELSEVIER

Vaccine 20 (2002) 1631–1639

Vaccine

www.elsevier.com/locate/vaccine

Early protection against homologous challenge after a single dose of replication-defective human adenovirus type 5 expressing capsid proteins of foot-and-mouth disease virus (FMDV) strain A24

M.P. Moraes, G.A. Mayr, P.W. Mason, M.J. Grubman*

US Department of Agriculture, Agricultural Research Service, Plum Island Animal Disease Center, North Atlantic Area, P.O. Box 848, Greenport, NY 11944-0848, USA

Received 20 August 2001; received in revised form 7 November 2001; accepted 9 November 2001

- ***Swine vaccinated IM at 1 site with $5x10^9$ pfu single dose of Ad5-A24 are protected from challenge as early as 7 dpv***

ELSEVIER

Available online at www.sciencedirect.com

SCIENCE DIRECT®

Virology 337 (2005) 205 – 209

VIROLOGY

www.elsevier.com/locate/yviro

Rapid Communication

Rapid protection of cattle from direct challenge with foot-and-mouth disease virus (FMDV) by a single inoculation with an adenovirus-vectored FMDV subunit vaccine

Juan M. Pacheco[a,b], Mario C.S. Brum[a], Mauro P. Moraes[c], William T. Golde[a], Marvin J. Grubman[a,*]

- ***Cattle vaccinated IM at 1 site with $5x10^9$ pfu of Ad5-A24 are protected from challenge as early as 7 dpv***

USDA

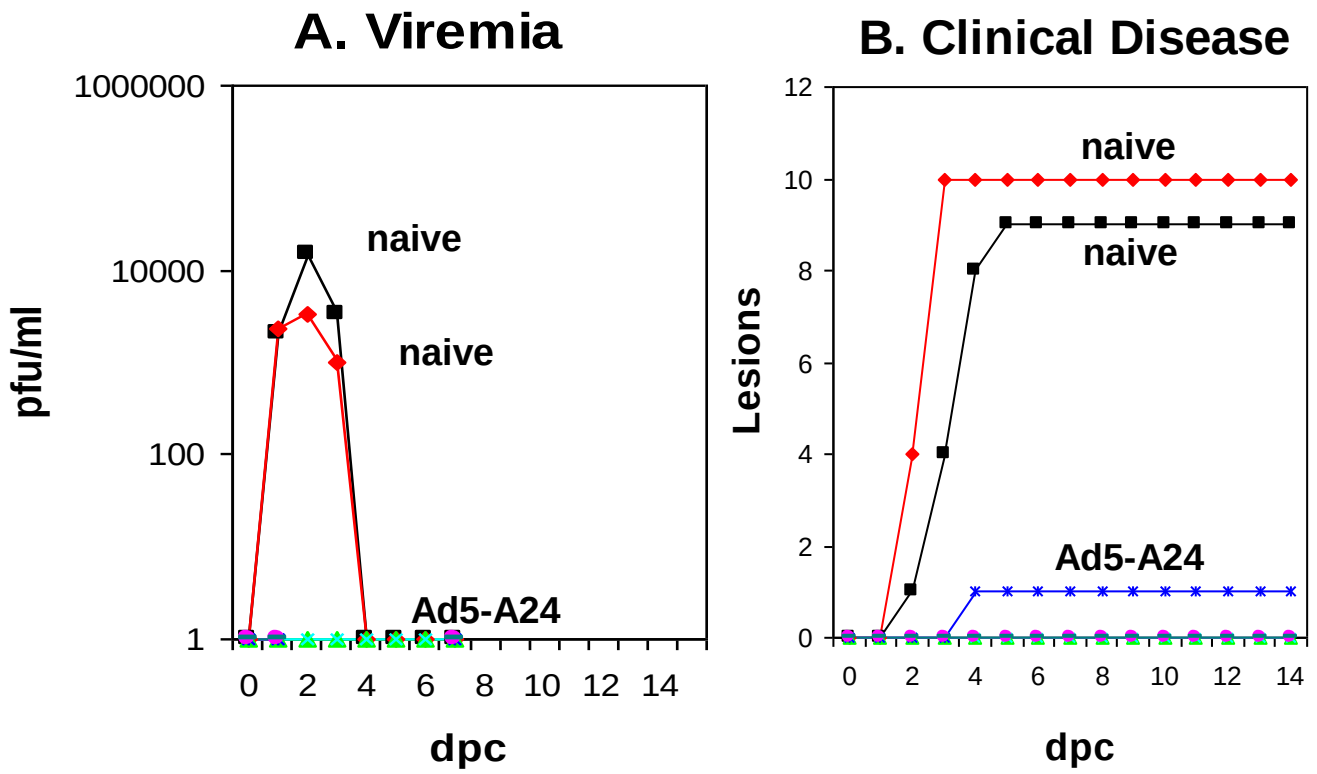
Efficacy of Ad5-A24 Vaccine in Swine

Vaccine	Boost	Challenge	Mean Neut Ab (0 dpc)	Viremia (3 dpc)	Protection
Control – 1	No	42 dpv	<8	Yes	Severe disease
Commercial Vaccine – 2	No	14 dpv	700	None	No disease
Commercial Vaccine – 3	No	42 dpv	700	None	No disease
Ad5-A24 – 4	Yes	14 dpv	400	None	No disease
Ad5-A24 – 5	No	42 dpv	120	None	No disease
Ad5-A24 – 6	No	14 dpv	450	None	No disease
Ad5-A24 – 7	No	7 dpv	36	None	No disease

- ***Swine vaccinated IM at 1 site with $5x10^9$ pfu single dose of Ad5-A24 are protected from challenge as early as 7 dpv***

Moraes et al., 2002

Efficacy of Ad5-A24 Vaccine in Cattle



Cattle vaccinated IM at 1 site with 5x10^9 pfu of Ad5-A24 are protected from challenge as early as 7 dpv

Pacheco et al., 2005

Inclusion of FMDV non structural 2B improves Ad5-FMD efficacy in swine and cattle

Vaccine 26 (2008) 5689–5699

Contents lists available at ScienceDirect

Vaccine

journal homepage: www.elsevier.com/locate/vaccine

Delivery of a foot-and-mouth disease virus empty capsid subunit antigen with nonstructural protein 2B improves protection of swine

Lindomar Pena[a], Mauro Pires Moraes[a], Marla Koster[a], Thomas Burrage[b], Juan M. Pacheco[a], Fayna Diaz-San Segundo[a], Marvin J. Grubman[a,*]

- ***More rapid FMDV-specific neutralizing Ab in swine.***
- ***All Ad5-FMD (A24-2B) vaccinated swine were protected from clinical disease and shedding as compared to 1st generation vaccine Ad5-FMD (A24)***

Vaccine 29 (2011) 9431–9440

Contents lists available at SciVerse ScienceDirect

Vaccine

journal homepage: www.elsevier.com/locate/vaccine

Increased efficacy of an adenovirus-vectored foot-and-mouth disease capsid subunit vaccine expressing nonstructural protein 2B is associated with a specific T cell response

Mauro Pires Moraes[a,b], Fayna Diaz-San Segundo[a,c], Camila C. Dias[a,c], Lindomar Pena[a,c,1], Marvin J. Grubman[a,*]

- ***Addition of 2B improves efficacy of Ad5-FMD (O1C) and enhances T-cell memory in cattle***

Improvement of potency in swine by inclusion of FMDV non structural 2B (Ad5-A24-2B)

- **Animals vaccinated with $5x10^9$ pfu Ad5 vector and challenged 21 days later.**
- **Very severe challenge, ie., ~500-fold higher than recommended by OIE (one animal died)**

Vaccine	pig #	PRN_{70} titer	Clinical score Assessment on day 4	Clinical score Assessment on day 7	Virus shedding (day of onset, duration)	Viremia (day of onset, duration)
Ad5-Blue	07	< 8	dead	dead	1.0×10^4 (2,2)	1.85×10^6 (1,3)
Ad5-Blue	08	< 8	11	11	8.5×10^2(1,4)	8.75×10^3 (2,2)
Ad5-A24	13	128	5	5	6.75×10^1(3,2)	0 (0,0)
Ad5-A24	14	128	5	5	2.28×10^2(3,2)	0 (0,0)
Ad5-A24	15	32	0	0	6.75×10^1(2,3)	0 (0,0)
Ad5-A24-2B	16	128	0	0	0 (0,0)	0 (0,0)
Ad5-A24-2B	17	128	0	0	0 (0,0)	0 (0,0)
Ad5-A24-2B	18	128	0	0	0 (0,0)	0 (0,0)

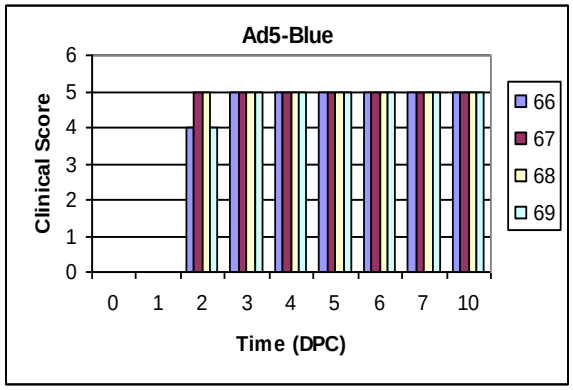
- ***More rapid FMDV-specific neutralizing Ab response.***
- ***All Ad5-A24-2B vaccinated animals were protected from clinical disease and virus shedding as compared to 1st generation vaccine.***

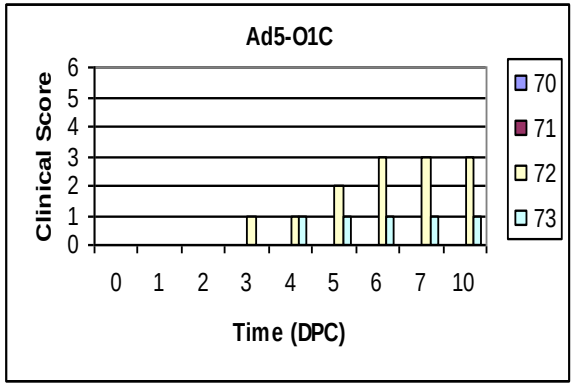
Pena et al., 2008

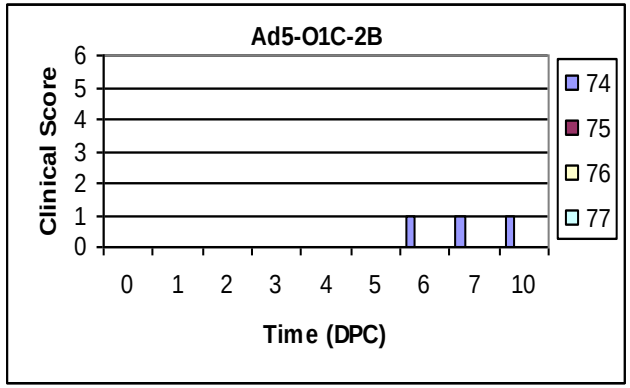
Improvement of potency in cattle by inclusion of FMDV non structural 2B (Ad5-O1C-2B)

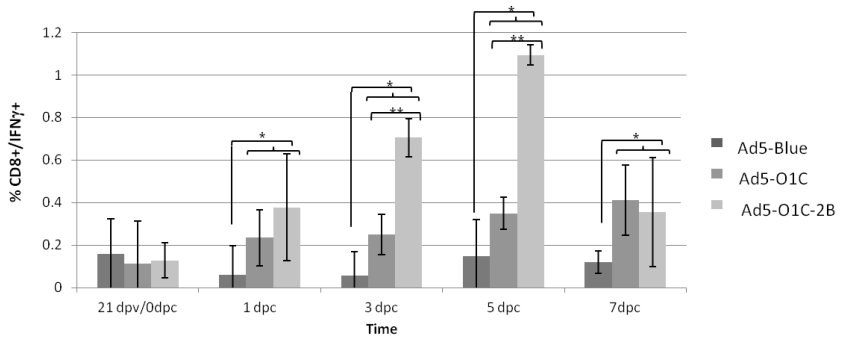
- FMDV O1 Campos is a highly virulent virus. Inactivated O vaccine generally requires 5-fold more antigen than type A vaccines to induce protection.

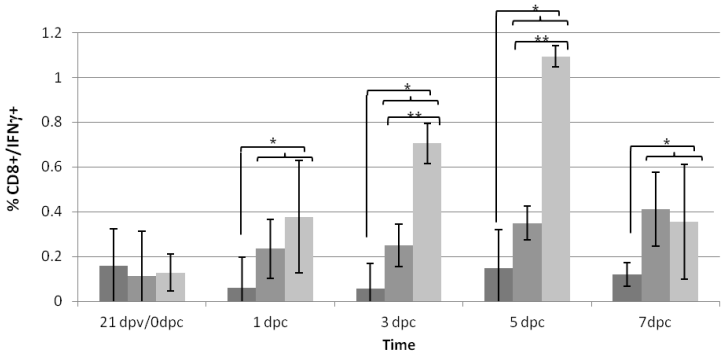
- Vaccinated animals with $5x10^9$ pfu Ad5-vectors and challenged 21 dpv











Ad5-O1C vaccination results in T cell memory response.
Addition of 2B enhances memory response

Moraes, Diaz-San Segundo et al 2011

Changing route of inoculation or using molecular adjuvants improves efficacy of Ad5-FMD (A24-2B) in swine

Review

Future Virology

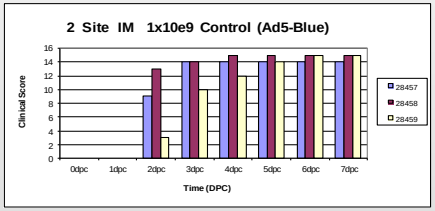
2012

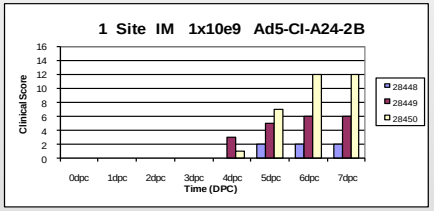
Adenovirus serotype 5-vectored foot-and-mouth disease subunit vaccines: the first decade

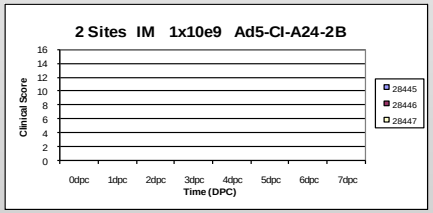
Marvin J Grubman†, Mauro P Moraes, Christopher Schutta, Jose Barrera, John Neilan, Damodar Ettyreddy, Bryan T Butman, Douglas E Brough & David A Brake

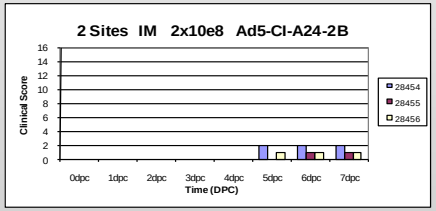
†Author for correspondence: USDA, ARS, NAA, Plum Island Animal Disease Center, PO Box 848, Greenport, NY 11944, USA ▪ Tel.: +1 631 323 3329 ▪ Fax: +1 631 323 3006 ▪ marvin.grubman@ars.usda.gov

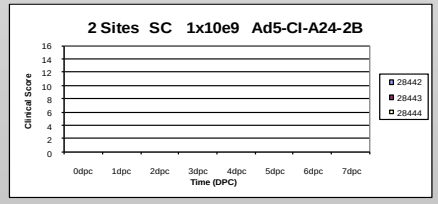
The results of the first decade of the development of a replication-defective human adenovirus serotype 5 (Ad5) containing the capsid- and 3C protease-coding regions of foot-and-mouth disease (FMD) virus as a vaccine candidate are presented. In proof-of-concept studies, it was demonstrated that a single inoculation

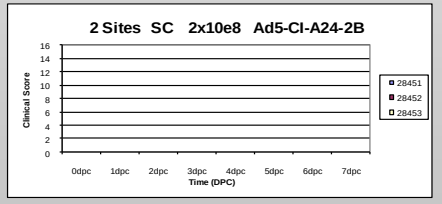












- ***Changing route and number of sites of inoculationallows 25x dose sparing of Ad5-A242B in swine***

Virology 468-470 (2014) 283–292

Contents lists available at ScienceDirect

Virology

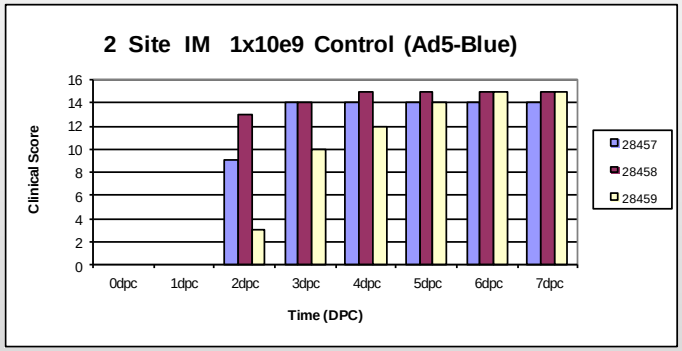
journal homepage: www.elsevier.com/locate/yviro

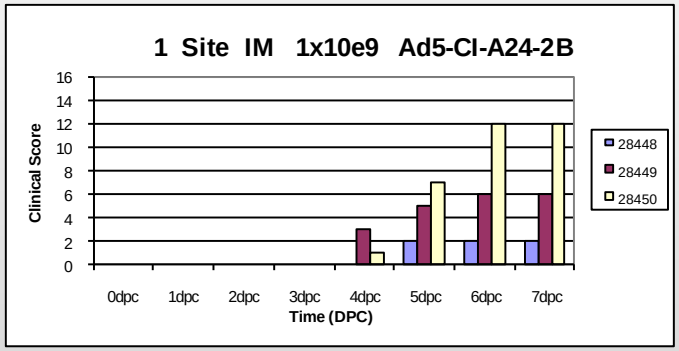
Poly ICLC increases the potency of a replication-defective human adenovirus vectored foot-and-mouth disease vaccine

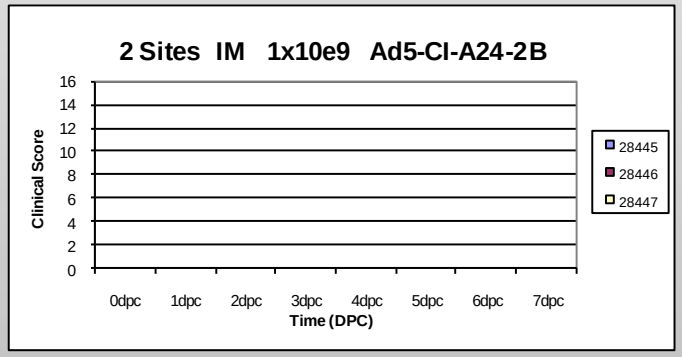
Fayna Diaz-San Segundo [a,1], Camila C. Dias [a,b,1], Mauro P. Moraes [a,c,2], Marcelo Weiss [a,b], Eva Perez-Martin [a,b], Andres M. Salazar [d], Marvin J. Grubman [a,*], Teresa de los Santos [a,*]

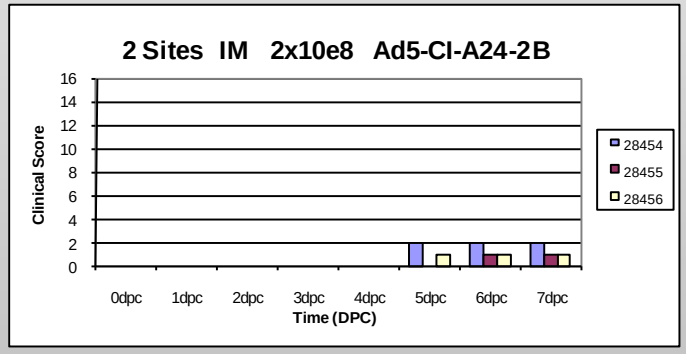
- ***Use of polyICLC allows 100x dose reduction of Ad5-A242B in swine.***

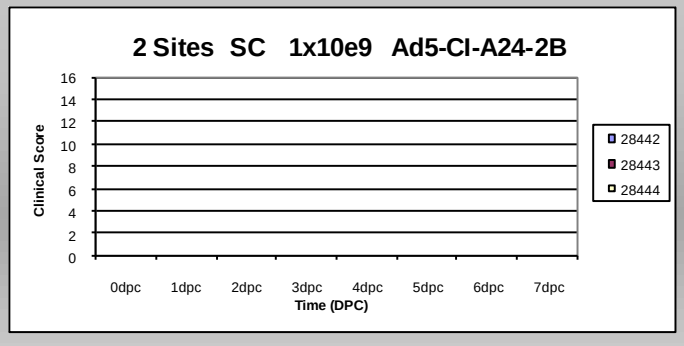
Changing route and number of sites of inoculation allows 25x dose sparing of Ad5-A242B in swine

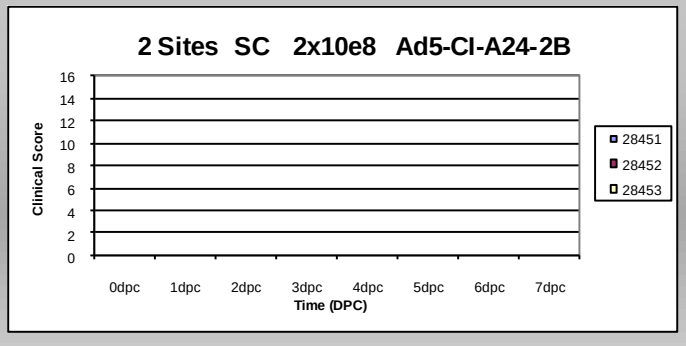












Grubman et al, 2012

Use of polyICLC allows 100x Ad5-A242B dose reduction to fully protect swine.

Vaccine	Dose (PFU)	Adjuvant	Animal #	Viremia	Shedding Virus	Clinical Score	SN	3ABC ELISA	RT-PCR	3D (RIP)
Ad5-Blue	$2x10^8$	-	16	$1/6.0x10^6/4$	$2/1.6x10^4/4$	2/15	0.1/2.7	SP	SP	SP
			17	$1/6.3x10^6/3$	$2/1.4x10^3/2$	2/13	0.1/D	D	SP	D
			18	$1/6.7x10^6/3$	$2/7.8x10^4/2$	2/17	0.1/D	D	SP	D
Ad5-CI-A24-2B	$2x10^8$	-	1	0	0	0	1.8/2.1	N	N	N
			2	0	0	0	2.7/3.3	SP	N	N
			3	0	0	0	2.1/2.4	N	N	N
Ad5-CI-A24-2B	$1x10^7$	-	13	0	$3/1.1x10^3/4$	4/2	1.8/2.7	WP	SP	SP
			14	$4/5.5x10^2/1$	$2/6.5x10^2/4$	3/17	0.1/2.7	SP	SP	WP
			15	$4/3.0x10^2/1$	$3/1.3x10^3/2$	3/15	1.2/3.0	SP	SP	SP
Ad5-CI-A24-2B	$1x10^7$	pICLC 1mg	10	0	0	0	1.5/2.4	N	N	N
			11	0	0	0	1.5/2.4	N	N	N
			12	0	0	0	1.2/3.0	N	N	N
Ad5-CI-A24-2B	$2.5x10^6$	pICLC 1mg	31472	0	0	0	0/D	D	D	D
			31473	0	0	0	0/1.2	N	WP	N
			31474	0	0	0	0/1.2	N	WP	N

Diaz-San Segundo et al., 2014

Improved efficacy of Ad5-FMD O1Manisa-2B in swine

Clinical and Vaccine Immunology

Evaluation of a Fiber-Modified Adenovirus Vector Vaccine against Foot-and-Mouth Disease in Cattle

Gisselle N. Medina,[a] Nestor Montiel,[a,b] Fayna Diaz-San Segundo,[a] Diego Sturza,[a,b] Elizabeth Ramirez-Medina,[a,b] Marvin J. Grubman,[a] Teresa de los Santos[a]

- ***Incorporation of an extra RGD in the fiber does NOT affect Ad5-FMD efficacy in cattle***

Virology 502 (2017) 123–132

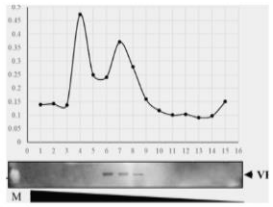
Contents lists available at ScienceDirect

Virology

journal homepage: www.elsevier.com/locate/yviro

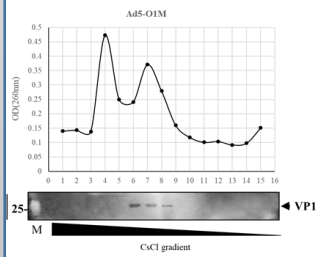
Adenovirus-vectored foot-and-mouth disease vaccine confers early and full protection against FMDV O1 Manisa in swine

Ignacio Fernandez-Sainz[a,b], Gisselle N. Medina[a,c], Elizabeth Ramirez-Medina[b,c], Marla J. Koster[a], Marvin J. Grubman[a], Teresa de los Santos[a,*]



- ***Ad5-FMD O1M -2B fully protects swine at 7 dpv using lower doses than those required for Ad5-FMD A24-2B***
- ***Good r values against FMDV O Mya 98 lineage***

Ad5-O1M2B fully protects swine even at lower doses than Ad5-A242B



Vaccine (dose)	Dose[a] (PFU)	Animal #	Viremia[c] dpc/max titer/duration	Shedding Virus[d] dpc/max titer/duration	Clinical Score[e]	SN[f] 0 dpc/21dpc	dpc/RT-PCR[g]
AdO1Man	$1x10^9$	39970	0	0	0	0.9/2.4	0
$1x10^9$ PFU		39971	0	0	0	0.9/1.8	0
21 dpv		39972	0	0	0	0.9/0.9	0
		39973	0	0	0	1.5/0.9	0
AdO1Man	$2x10^8$	39974	0	0	0	0.9/1.5	0
$2x10^8$ PFU		39975	0	0	0	1.5/1.8	0
21 dpv		39976	0	0	0	0.9/2.1	0
		39977	0	0	0	1.5/1.8	0
AdO1Man	$4x10^7$	39978	0	0	0	0.9/1.5	0
$4x10^7$ PFU		39979	0	0	0	1.2/1.8	0
21 dpv		39980	0	0	0	1.5/2.1	0
		39981	0	0	0	1.2/2.1	0
PBS	-	39982	$2/3.45x10^4/3$	$2/2.25x10^3/3$	2/16	0/2.1	2/WP/6
21 dpv		39983	$1/1.8x10^6/3$	$2/4.15x10^3/3$	3/16	0/1.8	2/WP/5
		39984	$1/1.65x10^6/3$	$2/3.3x10^3/3$	2/17	0/2.1	2/WP/6
		39985	$1/5.1x10^6/3$	$2/3.85x10^4/3$	2/17	0/2.4	2/WP/5

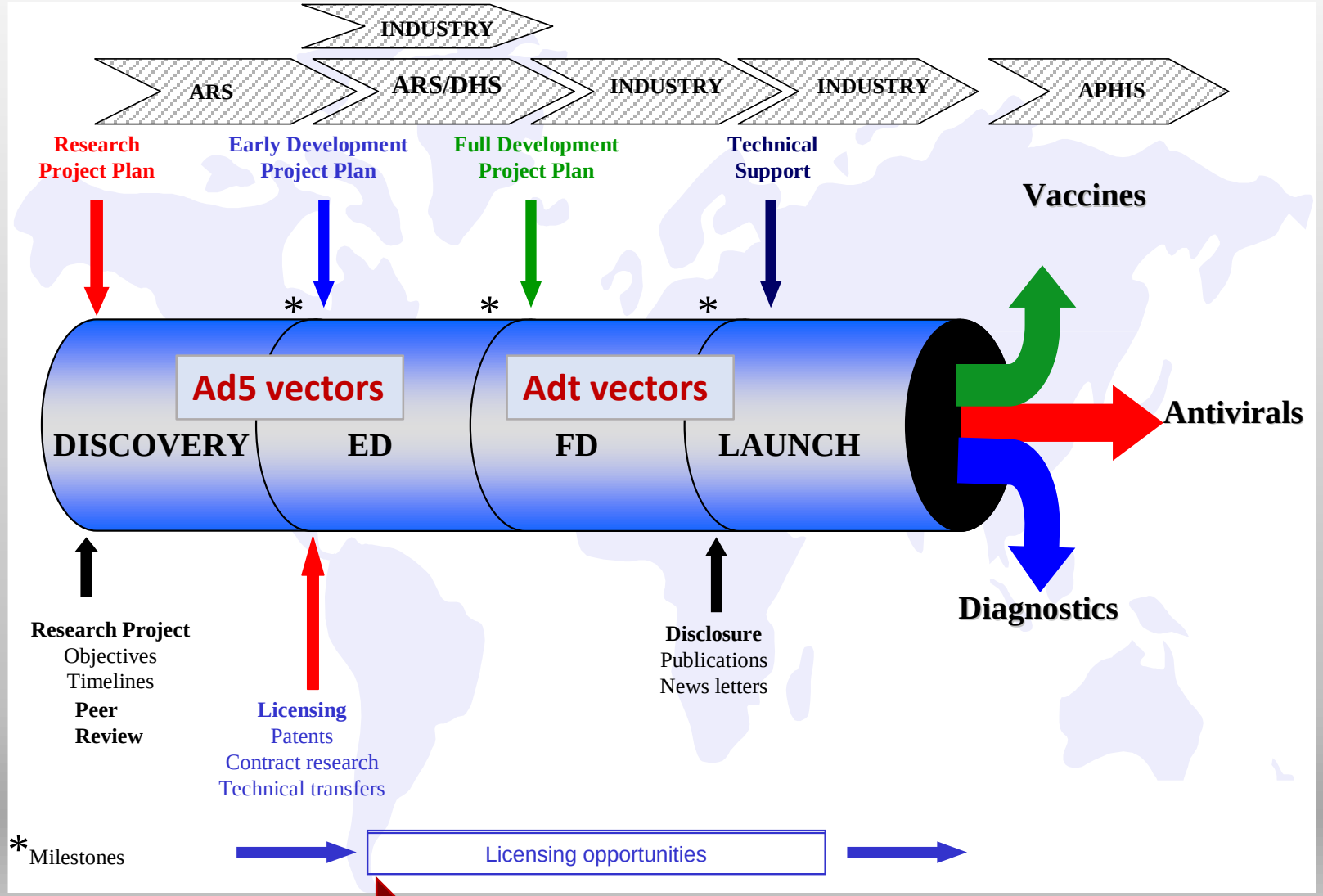
Fernandez-Sainz, Medina 2017

Summary: Ad5-FMD, early development

- Ad5-FMD vaccine induces protection (neutralizing antibody and cell-mediated immune responses) in swine and cattle with one dose
- Addition of full-length 2B coding region enhanced efficacy of Ad5-FMD vaccine
- SC inoculation at 2 sites enhanced potency vs IM
- Addition of adjuvant (polyICLC) further enhanced potency (100x dose sparing)
- Ad5-FMD vaccine demonstrated efficacy against FMDV A24, O1C and O1M

USDA

Ad5- and Adt- FMD product development



Similarities and Differences between "Ad5" and "Adt"-based FMD vaccines

"Ad5" (Ad5 Blue)

- *Commercially* available off-the shelf human adenovirus serotype 5 research vector
- Replication-deficient in host
- E1/E3 gene deleted; replicates in HEK 293 cell line
- Used by USDA ARS for FMD vaccine translational research
- Basis of all USDA ARS publications

"Adt"

- *Proprietary* human adenovirus serotype 5 vector for human and veterinary vaccine development
- Replication-deficient in host
- E1/E3/E4 gene deleted; replicates in specialized manufacturing cell lines (293-ORF6; M2A)
- Used by DHS S&T and industry partners for vaccine regulatory development and licensure
- Basis of all DHS S&T publications

Adt-FMD Platform - Publications

Jungback C (ed): Potency Testing of Veterinary Vaccines for Animals: The Way From in Vivo to in Vitro. Dev Biol (Basel). Basel, Karger, 2011, vol 134, pp 123-133.

Human Adenovirus-Vectored Foot-and-Mouth Disease Vaccines: Establishment of a Vaccine Product Profile Through in Vitro Testing

D.A. Brake[1], M. McIlhaney[2], T. Miller[2], K. Christianson[2], A. Keene[3], G. Lohnas[3], C. Purcell[3], J. Neilan[1], C. Schutta[1], J. Barrera[1] T. Burrage[1], D.E. Brough[3], B.T. Butman[3]

[1] United States Department of Homeland Security, Science & Technology, Plum Island Animal Disease Center, Greenport, NY, USA.
[2] Benchmark Biolabs Inc., Lincoln, NE, USA.
[3] GenVec, Inc., Gaithersburg, MD, USA.

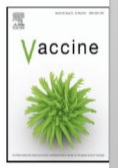
- Indirect, SVN-based serology test for Adt-A24 vaccine lot release is not feasible using 7dpv serum
- AE-HPLC can be used as an in-process assay to monitor Adt-FMD yields.
- Developed Western blot assay offers potential for use as an in vitro potency test for lot release
- PU assay can be used for assessment of long-term vaccine stability

Vaccine 34 (2016) 3214–3220

Contents lists available at ScienceDirect

Vaccine

journal homepage: www.elsevier.com/locate/vaccine

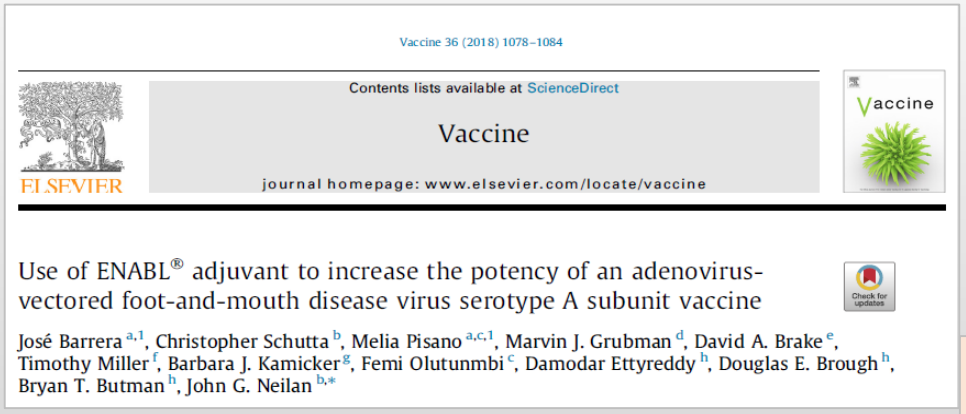


Multiple efficacy studies of an adenovirus-vectored foot-and-mouth disease virus serotype A24 subunit vaccine in cattle using homologous challenge

Christopher Schutta[a], José Barrera[b,1], Melia Pisano[b,c,1], Laszlo Zsak[a,2], Marvin J. Grubman[d], Gregory A. Mayr[d,3], Mauro P. Moraes[d,4], Barbara J. Kamicker[e], David A. Brake[e], Damodar Ettyreddy[f], Douglas E. Brough[f], Bryan T. Butman[f], John G. Neilan[a,*]

- Adt-FMD A24 is safe after IM dosing (8 studies, 150 steers)
- Immunogenic; antibody titers dose dependent.
- Adt-A24 protected cattle from clinical disease and viremia after FMDV A24 challenge at 7 dpv.
- Adt-A24 was a DIVA vaccine absence of NSP antibodies post vaccination.
- Non-vaccinated animals co-mingled with Adt-FMD A24 vaccinates did not seroconvert to Adt vector

Adt-FMD Platform - Publications



Vaccine 36 (2018) 1078–1084

Contents lists available at ScienceDirect

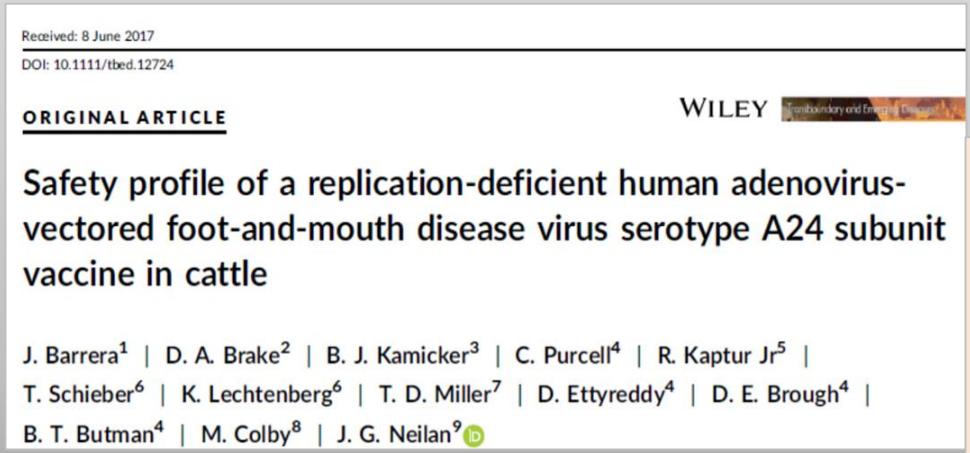
Vaccine

journal homepage: www.elsevier.com/locate/vaccine

Use of ENABL® adjuvant to increase the potency of an adenovirus-vectored foot-and-mouth disease virus serotype A subunit vaccine

José Barrera[a,1], Christopher Schutta[b], Melia Pisano[a,c,1], Marvin J. Grubman[d], David A. Brake[e], Timothy Miller[f], Barbara J. Kamicker[g], Femi Olutunmbi[c], Damodar Ettyreddy[h], Douglas E. Brough[h], Bryan T. Butman[h], John G. Neilan[b,*]

- **Inclusion of ENABL® in Adt-FMD vaccine formulation allows for 19x dose sparing (based on Bovine Protective Dose $_{50}$ of 3x10^{10}PU (76 steers)**



Received: 8 June 2017

DOI: 10.1111/tbed.12724

ORIGINAL ARTICLE

WILEY

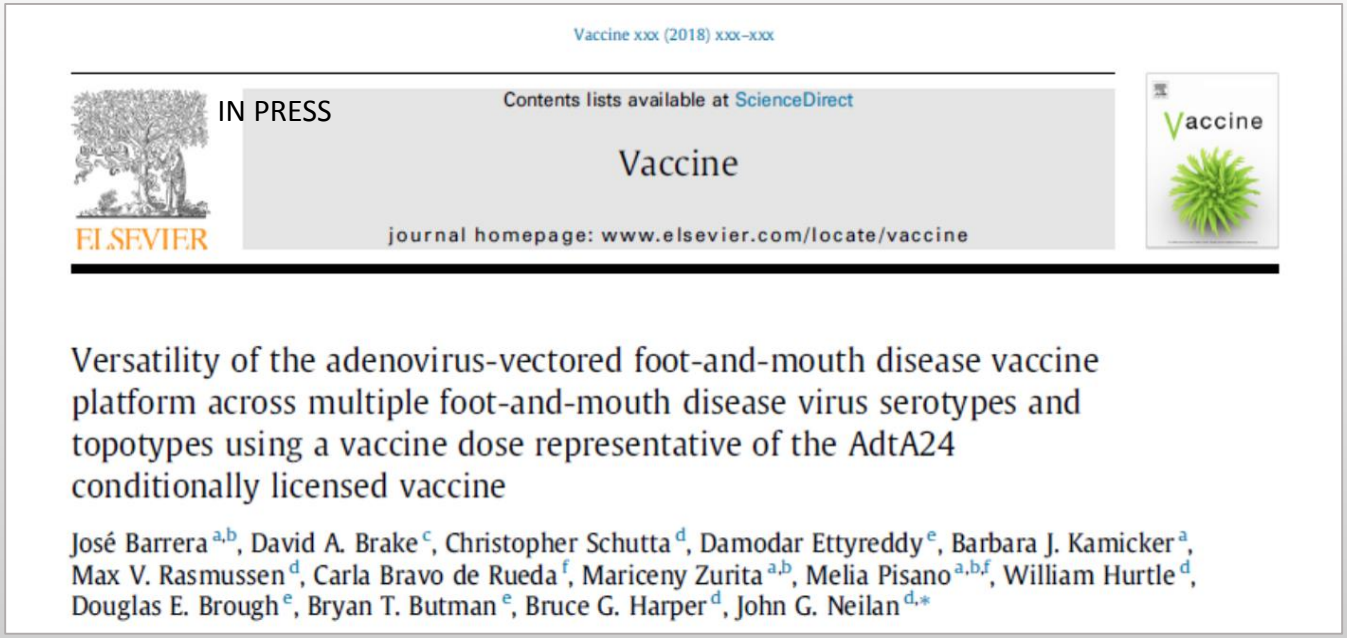
Safety profile of a replication-deficient human adenovirus-vectored foot-and-mouth disease virus serotype A24 subunit vaccine in cattle

J. Barrera[1] | D. A. Brake[2] | B. J. Kamicker[3] | C. Purcell[4] | R. Kaptur Jr[5] | T. Schieber[6] | K. Lechtenberg[6] | T. D. Miller[7] | D. Ettyreddy[4] | D. E. Brough[4] | B. T. Butman[4] | M. Colby[8] | J. G. Neilan[9]

- **3 studies with a total of 22 cattle demonstrated that the AdtA24 master seed virus (MSV) was safe, did not revert to virulence and was not shed or spread from vaccinees to susceptible cattle or pigs.**
- **One study 10 lactating cows : Adt-A24 was completely absent from milk.**
- **One study under typical U.S. production field with 500 healthy beef and dairy cattle using two AdtA24 vaccine serials**

AdtA24 fulfills safety-related requirements for U.S. regulatory requirements.

Adt-FMD Platform - Publications



Vaccine xxx (2018) xxx–xxx

IN PRESS

Contents lists available at ScienceDirect

Vaccine

journal homepage: www.elsevier.com/locate/vaccine

Versatility of the adenovirus-vectored foot-and-mouth disease vaccine platform across multiple foot-and-mouth disease virus serotypes and topotypes using a vaccine dose representative of the AdtA24 conditionally licensed vaccine

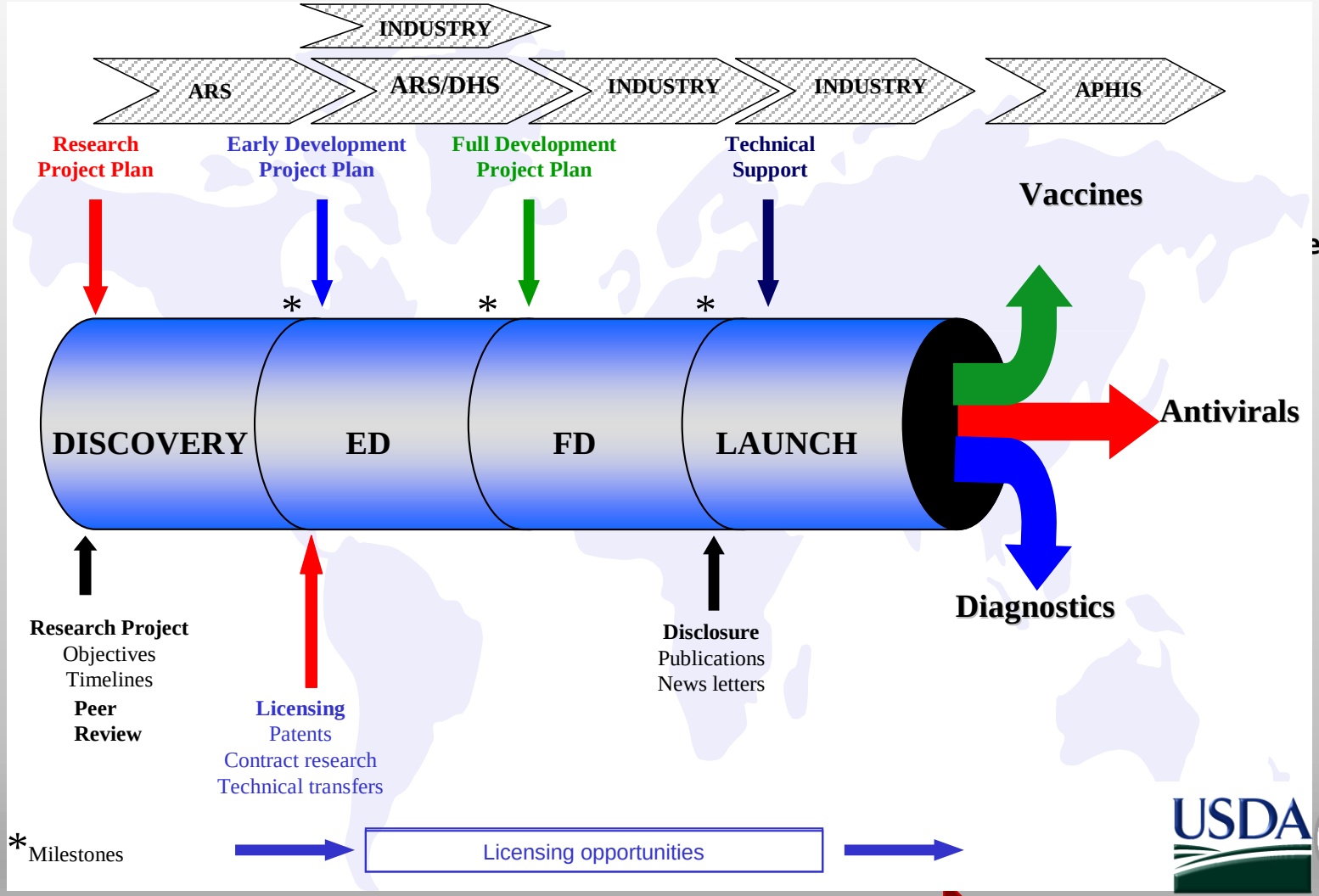
José Barrera[a,b], David A. Brake[c], Christopher Schutta[d], Damodar Ettyreddy[e], Barbara J. Kamicker[a], Max V. Rasmussen[d], Carla Bravo de Rueda[f], Mariceny Zurita[a,b], Melia Pisano[a,b,f], William Hurtle[d], Douglas E. Brough[e], Bryan T. Butman[e], Bruce G. Harper[d], John G. Neilan[d,*]

- **The Adt-FMD vaccine platform is versatile for multiple FMDV serotypes and topotypes (22 studies, 375 bovines)**
- **Cattle were immunized with one of 16 different Adt-FMD monovalent vaccines**
- **All Adt-FMD monovalent vaccines elicited FMDV neutralizing antibodies in cattle.**
- **All Adt-FMD monovalent vaccines protected cattle against homologous FMDV challenge**
- **Cattle studies were conducted using a commercially viable Adt-FMD vaccine dose.**

Adt-FMD Summary (full development)

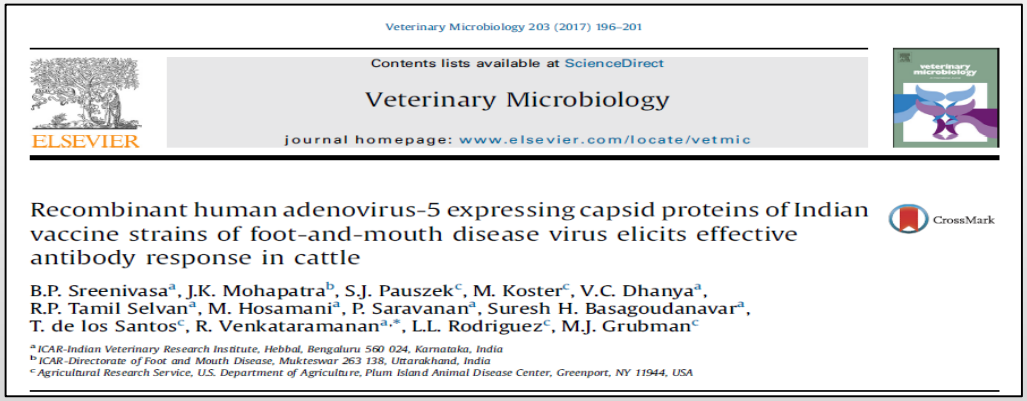
- **A product profile for Adt-A24 vaccine was successfully established**
- **Multiple efficacy studies involving at least 150 vaccinated steers. non-adjuvanted Adt-A24 experimental vaccine was shown to be safe, immunogenic, consistently protected cattle at 7 dpv against homologous FMDV challenge, and enabled DIVA**
- **Addition of adjuvant ENABL® further enhanced potency of Adt-A24. 19X dose sparing based on BPD_{90} (76 steers)**
- **Adt-A24 passed strict safety tests: 1) no reversion to virulence or transmission in 22 cattle and swine. 2) No secretion in milk of 10 lactating cows. 3) Evaluated under commercial beef and dairy production farm settings in 500 cattle.**
- **Adt5-FMD vaccine platform was proven efficacious for 16 different subtypes including A, O, Asia, SAT2 and SAT3 serotypes (375 bovines)**

Ad5 FMD product development



Adt5-FMD A24 Cru licensed in USA

Replication deficient human adenovirus vectored FMD vaccines - CHALLENGES

1. 

Veterinary Microbiology 203 (2017) 196–201

Contents lists available at ScienceDirect

Veterinary Microbiology

journal homepage: www.elsevier.com/locate/vetmic

Recombinant human adenovirus-5 expressing capsid proteins of Indian vaccine strains of foot-and-mouth disease virus elicits effective antibody response in cattle

B.P. Sreenivasa[a], J.K. Mohapatra[b], S.J. Pauszek[c], M. Koster[c], V.C. Dhanya[a], R.P. Tamil Selvan[a], M. Hosamani[a], P. Saravanan[a], Suresh H. Basagoudanavar[a], T. de los Santos[c], R. Venkataramanan[a,*], L.L. Rodriguez[c], M.J. Grubman[c]

[a] ICAR-Indian Veterinary Research Institute, Hebbal, Bengaluru 560 024, Karnataka, India
[b] ICAR-Directorate of Foot and Mouth Disease, Mukteswar 263 138, Uttarakhand, India
[c] Agricultural Research Service, U.S. Department of Agriculture, Plum Island Animal Disease Center, Greenport, NY 11944, USA

Polyvalent Ad5-FMD is less potent than monovalent Ad5-FMD in cattle

2. Vaccine coverage: intra/inter-serotype protection

3. 

Journal of Virology

The Foot-and-Mouth Disease Carrier State Divergence in Cattle

Carolina Stenfeldt,[a,b] Michael Eschbaumer,[a,b] Steven I. Rekant,[a,b] Juan M. Pacheco,[a] George R. Smoliga,[a] Ethan J. Hartwig,[a] Luis L. Rodriguez,[a] Jonathan Arzt[a]

Plum Island Animal Disease Center, Foreign Animal Disease Research Unit, Agricultural Research Service, United States Department of Agriculture, Greenport, New York, USA[a]; Oak Ridge Institute for Science and Education, PADC Research Participation Program, Oak Ridge, Tennessee, USA[b]

Adt5-FMD does not prevent persistence

4. Duration of immunity: 6 months likely. More studies required

5. Adt-FMD may not as effective as Ad5-FMD in swine

Ideal vaccine properties and Adt-FMD limitations

	Characteristics	Adt-FMD	Ideal vaccine
Efficacy:	Protective immunity after one dose	√	Yes
	Onset of protection (days post vaccination)	7-21	1
	Long-lasting immunity (>1 year)	?	Yes
	Cross-protection within serotype	No/Yes	Yes
	Cross protection across serotypes	No	Yes
	Prevents primary infection	√	Yes
	Prevents carrier state in ruminants	No	Yes
	Efficacious by multiple routes of inoculation	√	Yes
Safety:	Does not require high containment for manufacturing	√	Yes
	Safe in all target species	√	Yes
	Withdrawal for food consumption (days post vaccination)	√	<30
	Genetically stable (unable to revert-to-virulence)	√	Yes
Other	Development of relevant antigens against emerging strains	Months	Days/weeks
	Featured long shelf life (> 2 years)	√	Yes
	Intrinsic negative DIVA markers	√	Yes
	Cost	Moderate	Low
	Thermal stability	√	Yes

Thank you

John Neilan

Jose Barrera
David Brake
Chris Schutta
Max Rasmussen
Michael Puckette
Laszlo Zsak
Barbara Kamicker
Melia Pisano
Mereceny Zurita

Gisselle Medina
Paul Azzinaro
Joseph Gutkoska
Aishwarya Mogulothu

Luis Rodriguez

Jonathan Arzt
Bill Golde
James Zhu
Penny Berry

Marvin J. Grubman

Greg Mayr
Mauro Moraes
Lek Chinsangaram
Josh Wu
Lindomar Pena
Juan M. Pacheco
Camila Dias
Mario Brum
Nestor Montiel
Diego Sturza
Elizabeth Ramirez-Medina
Marcelo Weiss
Ignacio Fernandez-Sainz
Fayna Diaz-San Segundo

GenVec

Damodar Ettyreddy
Douglas E. Brough
Bryan T. Butman

VAXLIANT Advancing Vaccines

Oncovir, Inc.

PIADC Animal Research Unit

USDA

U.S. Department of Homeland Security