Summary of EMA non-clinical models workshop November 24/25 2025

IABS Workshop on RWE:

Alternative Approaches to Phase 3 Clinical Trials for Vaccine Efficacy and Licensure: the role of Real-World Evidence

10-11 December, Montreal, Canada

Dr. Marco Cavaleri

Head of Public Health Threats

Chair of the Emergency Task Force, EMA

EMA
EUROPEAN MEDICINES AGENCY

EMA workshop on non-clinical data for regulatory decision-making on the efficacy of medical countermeasures

24 – 25 November 2025, 9:00 -17:15 CEST

Hybrid workshop

Aims of the workshop

- Discuss the current regulatory frameworks for approval of medical countermeasures when no human efficacy studies can be conducted

- Building on examples from vaccines and therapeutics, review the translational outcomes of non-clinical data utilized in regulatory decisions as key evidence of efficacy

- Discuss how to: establish and choose non-clinical models that could reliably predict efficacy in humans; interpret and to bridge non-clinical results to expected clinical efficacy; identify success criteria for regulatory decision-making

- Review alternative approaches to the use of animal models and their potential for use in regulatory decision-making on medical countermeasures

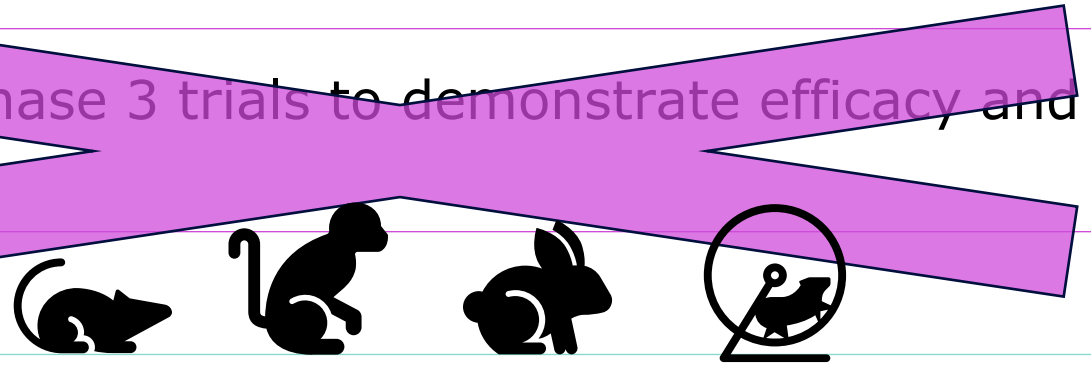
Session 1

- Current regulatory frameworks and requirements for accepting animal efficacy data as key evidence for efficacy in humans
- How to set up the right animal model for established and emerging infectious diseases
- Room for respecting 3Rs and improve this models to reduce animal studies as far as possible.
- Relevance to the human disease is important but may not be possible for all threats

EU approval based on non-clinical efficacy data

Not feasilble

- Phase 2 or Phase 3 trials to demonstrate efficacy and safety in humans



Feasible

Animal efficacy data as **pivotal evidence of efficacy** and extrapolation of dose and efficacy to humans

Requirements:

1. **Prevents/treats** a **serious, life-threatening** disease
2. **Complete CMC** and **non-clinical package** is available
3. **A relevant animal model** reflective of the human disease is available
4. **Efficacy** is demonstrated in **well-controlled animal efficacy studies**
5. **Clinical trials** on safety, pharmacokinetic and pharmacodynamic data in humans and animals → **allow selection** of an **effective dose in humans**
6. MCM is **reasonably likely** to **provide a clinical benefit** in **humans**
7. **Specific obligations** to conduct a PAES, in case of an outbreak

EMA position

Preparedness against **serious public health threats** → paramount and of **utmost importance**

EMA **supports developers** of **MCMs** for serious public health threats including CBRN agents

Flexible regulatory approaches can be **applied** for serious public health threats

Marketing authorisation type will be decided on **case-by-case and dependent on:**

- **Comprehensiveness** of **available data** at the time of MAA
- **Likelihood** of collecting of **comprehensive data post-marketing**

Seek **EMA ETF advice** early in clinical development

- Whether the **product qualifies** for **flexible regulatory approaches**
- **Development program** of the MCM
- **Choice, development** and **relevance** of the **animal model** for demonstrating of efficacy

The US FDA Animal Rule

Scope: The Animal Rule can be used only when all of these circumstances are met

The product is intended to ameliorate or prevent a serious or life-threatening condition caused by exposure to a lethal or permanently disabling toxic chemical, biological, radiological or nuclear (CBRN) substance	Definitive human efficacy studies cannot be conducted because deliberate exposure of healthy volunteers to the lethal or permanently disabling toxic CBRN substance would be unethical	Field trials to study effectiveness of the product after an accidental or hostile exposure to the CBRN substance have not been feasible	The product cannot be approved or licensed for the proposed indication based on efficacy standards described in other parts of the regulations

The product has been studied for safety

From 21 CFR 314.600 for drugs; 21 CFR 601.90 for biologics

www.fda.gov

EMA

The US FDA Animal Rule

1. There is a reasonably well-understood pathophysiological mechanism of the toxicity of the substance and its prevention or substantial reduction by the product

2. The effect is demonstrated in more than one animal species expected to react with a response predictive for humans, unless the effect is demonstrated in a single animal species that represents a sufficiently well-characterized animal model for predicting the response in humans

All four criteria must be met

3. The animal study endpoint is clearly related to the desired benefit in humans, generally the enhancement of survival or prevention of major morbidity

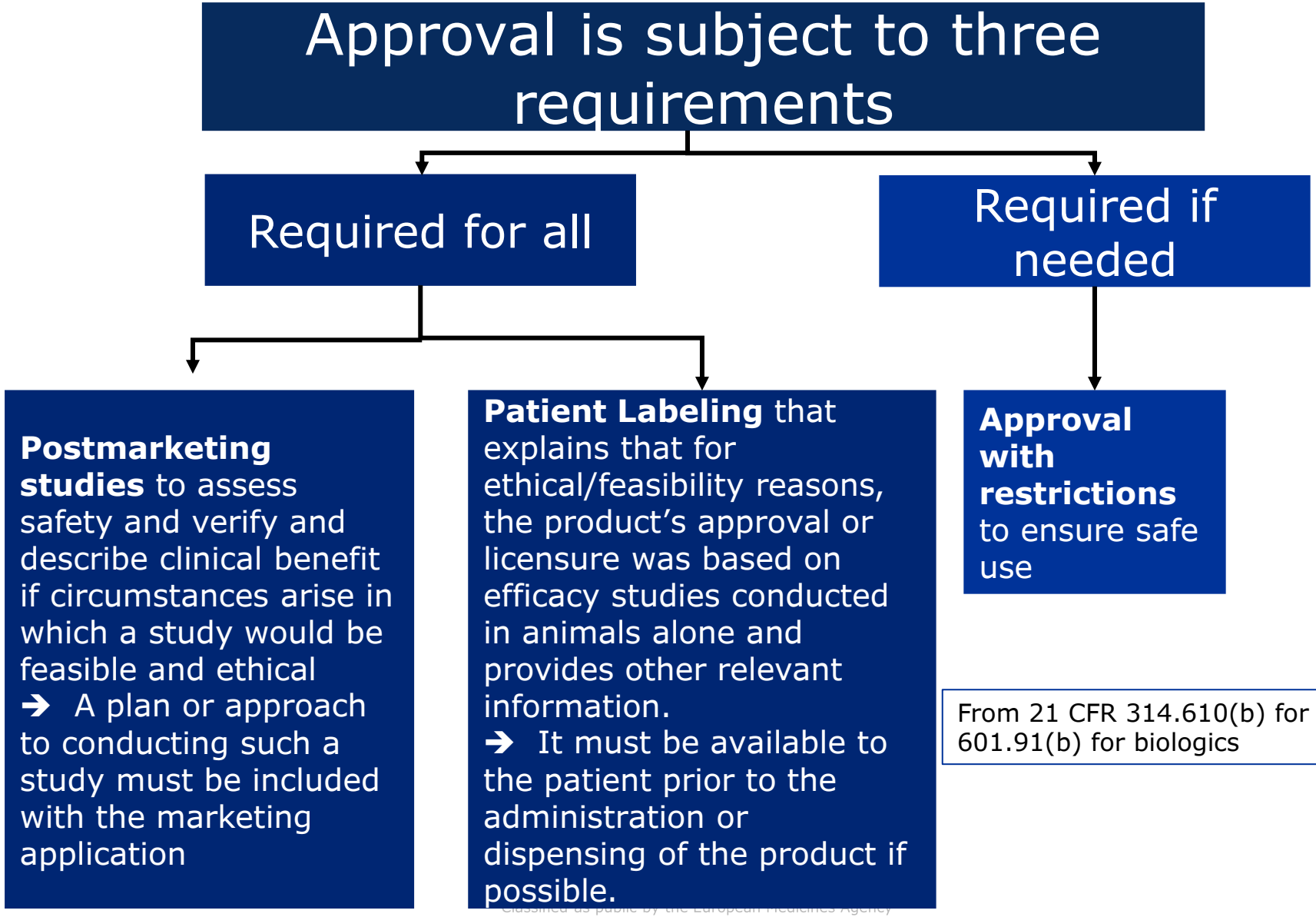
4. The data or information on the kinetics and pharmacodynamics of the product or other relevant data or information, in animals and humans, allows selection of an effective dose in humans

Quoted from 21 CFR 314.610(a) for drugs; 21 CFR 601.91(a) for biologics

www.fda.gov

EMA

The US FDA Animal Rule



From 21 CFR 314.610(b) for drugs; 21 CFR 601.91(b) for biologics

www.fda.gov

Common limitations of animal models

- Require adaptation of pathogens
- Require partially immune-compromised animals
- Do not have appropriate receptors or receptor distribution
- Induce different immune responses to humans
  - Different kinetics of innate and adaptive responses
  - Immune repertoire and TLR distribution
  - Differ in mucosal and systemic immune response
- Require non-physiological challenge doses and routes
- Cost, availability, reagents

Non-human primate models are usually the best animal models to replicate human disease

- **For efficacy demonstration, animal model data should be used in conjunction with other datasets to best inform regulatory decision-making**
- **It's the totality of the data that should be considered**

EMA

Define route, strain and challenge dose

- Whenever possible use physiologically relevant challenge routes to induce measurable disease
  - E.g. IN and/or aerosol for respiratory infections
  - Highly artificial challenge routes (e.g IP or IC) not very useful to predict efficacy
- Ideally use clinical isolates (minimally passaged and whose sequence has been confirmed and standardized) as challenge strains
- Conduct dose-down studies to discover lowest possible dose to induce physiologically relevant disease
  - Large challenge doses are unnatural and can overcome immunity of vaccines that under normal, real-life situations would be protective

Standardize the animal model for reproducibility

The Filovirus Animal Non-clinical Working Group
(FANG)
Ebola NHP Model
Standardization Effort (2011-2019)

Development of Well Characterized Challenge Material (WCCM)

Strain Selection

Regulatory perspective

USG 2012 data call

CDC Seed Stocks

Key selection criteria

Production & Distribution

Standardized growth protocol

Master & Working Viral Banks

Stocks Available in BEI Resources

Release, Characterization, Stability Assays

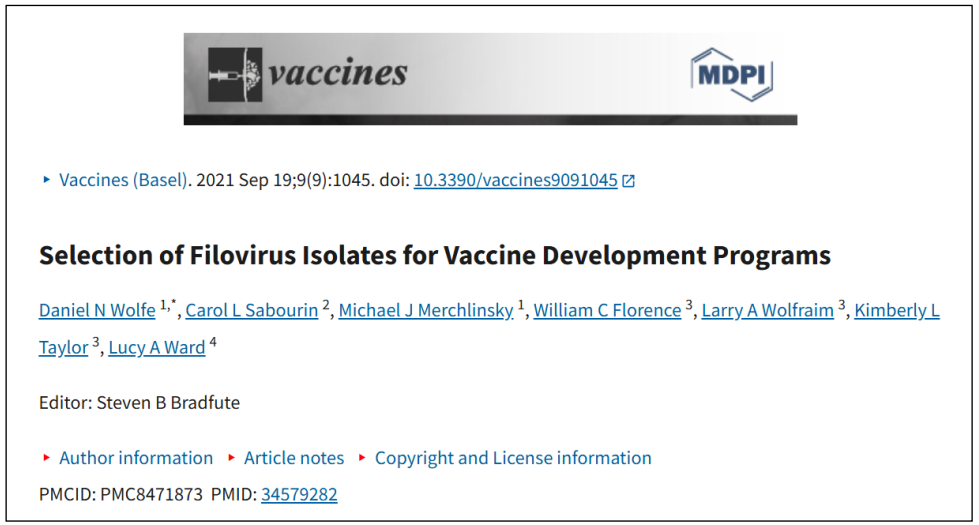
Standardized assays, i.e.

Plaque and TCID50

NGS

7U vs 8U

Certificate of Analysis



vaccines MDPI

Vaccines (Basel). 2021 Sep 19;9(9):1045. doi: 10.3390/vaccines9091045

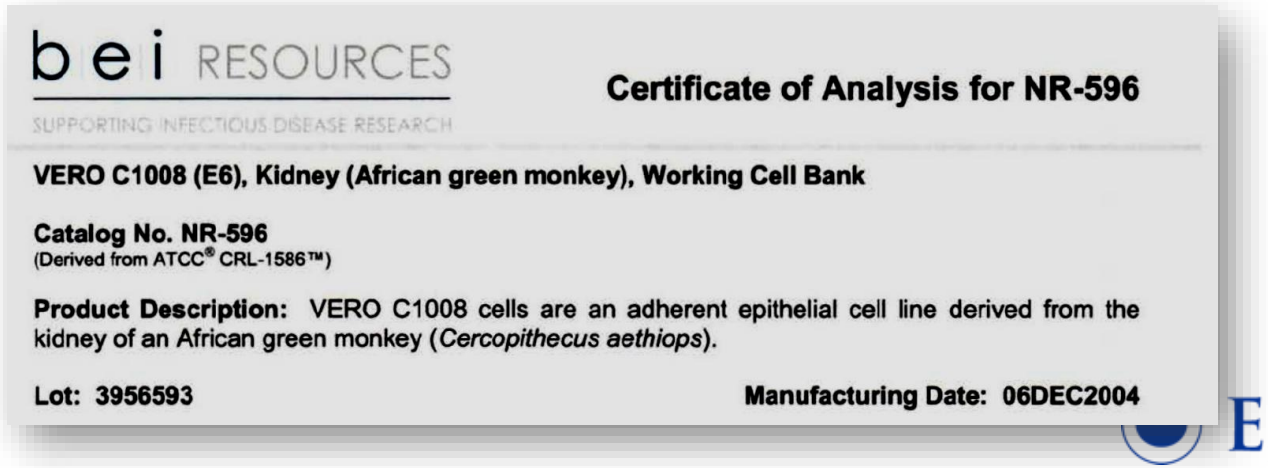
Selection of Filovirus Isolates for Vaccine Development Programs

Daniel N Wolfe [1,*], Carol L Sabourin [2], Michael J Merchlinsky [1], William C Florence [3], Larry A Wolfraim [3], Kimberly L Taylor [3], Lucy A Ward [4]

Editor: Steven B Bradfute

Author information · Article notes · Copyright and License information

PMCID: PMC8471873 PMID: 34579282



bei RESOURCES

SUPPORTING INFECTIOUS DISEASE RESEARCH

Certificate of Analysis for NR-596

VERO C1008 (E6), Kidney (African green monkey), Working Cell Bank

Catalog No. NR-596
(Derived from ATCC® CRL-1586™)

Product Description: VERO C1008 cells are an adherent epithelial cell line derived from the kidney of an African green monkey (*Cercopithecus aethiops*).

Lot: 3956593 **Manufacturing Date: 06DEC2004**

EMA

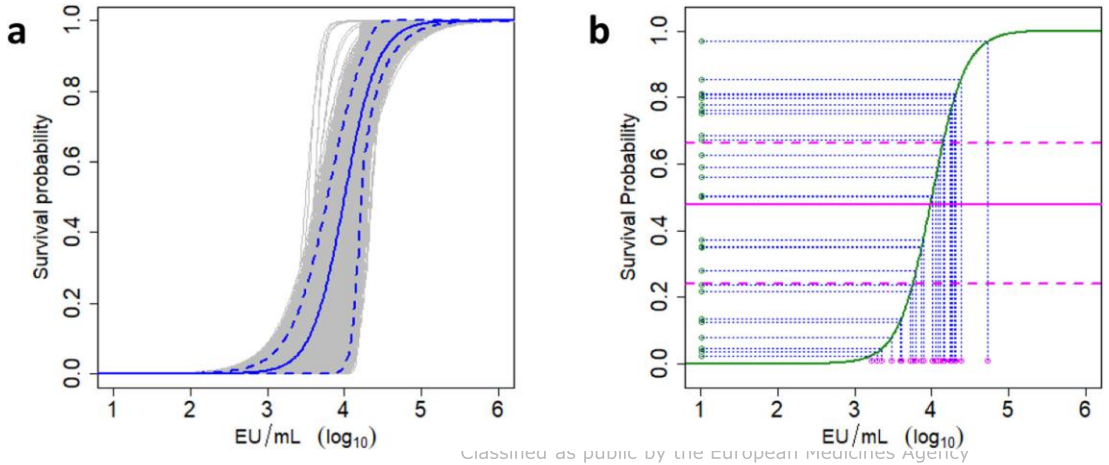
Considerations for bridging between animal models and humans

1. Bounds of durability can be estimated with NHP challenges but possibly not with antibody titers
2. Durability of protection in NHP may be predictive of durability in humans (the NHP/Human vaccine protection and durability relationship is reasonably predictive for SARS-CoV-2)
3. Antibody correlate of protection is context dependent and empirical
    - Antigen composition (monovalent vs. bivalent vs. multivalent)
    - Vaccine platform and regimen
    - Pre-existing vector immunity
    - Quantitative correlate changes with interval between vaccination and challenge
4. Animal model challenge dose and route should be optimized for bridging to humans - more is not better and may misrepresent normal human exposure immune responses

Ebola: Pre-clinical data that led to the approval of Zabdeno/Mvabea

FDA- and EMA-approved immunobridging strategy: inferring clinical benefit

- Use curve to calculate mean survival probability and 95% CI in humans using double-bootstrap method
- Clinical benefit demonstrated if lower limit of 95% CI is above pre-specified success criterion of 20% (FDA- and EMA-approved)
- NHP model more stringent than EVD in humans:
  - Model can provide evidence for clinical benefit
  - Model cannot quantify vaccine effectiveness, as 1:1 translation will likely underestimate clinical benefit
- Quantification of the actual clinical effectiveness must be determined in a field study



Roozendaal et al, NPJ Vacc 2020

Ebola: Pre-clinical data that led to the approval of Zabdeno/Mvabea

Immuno-bridging Statistical Analysis

Final Immuno-bridging (PPS) Final Primary analysis	
Per Protocol Immunogenicity Analysis Set	**Ad26.ZEBOV, MVA-BN-Filo (0,56)**
N	1550
Mean Predicted Survival Probability (95.7% CI)	57.3% (**41.2%** ; 71.0%)

The 95.7% CI lower limit of **41.2% passes the pre-specified success criterion of 20%**

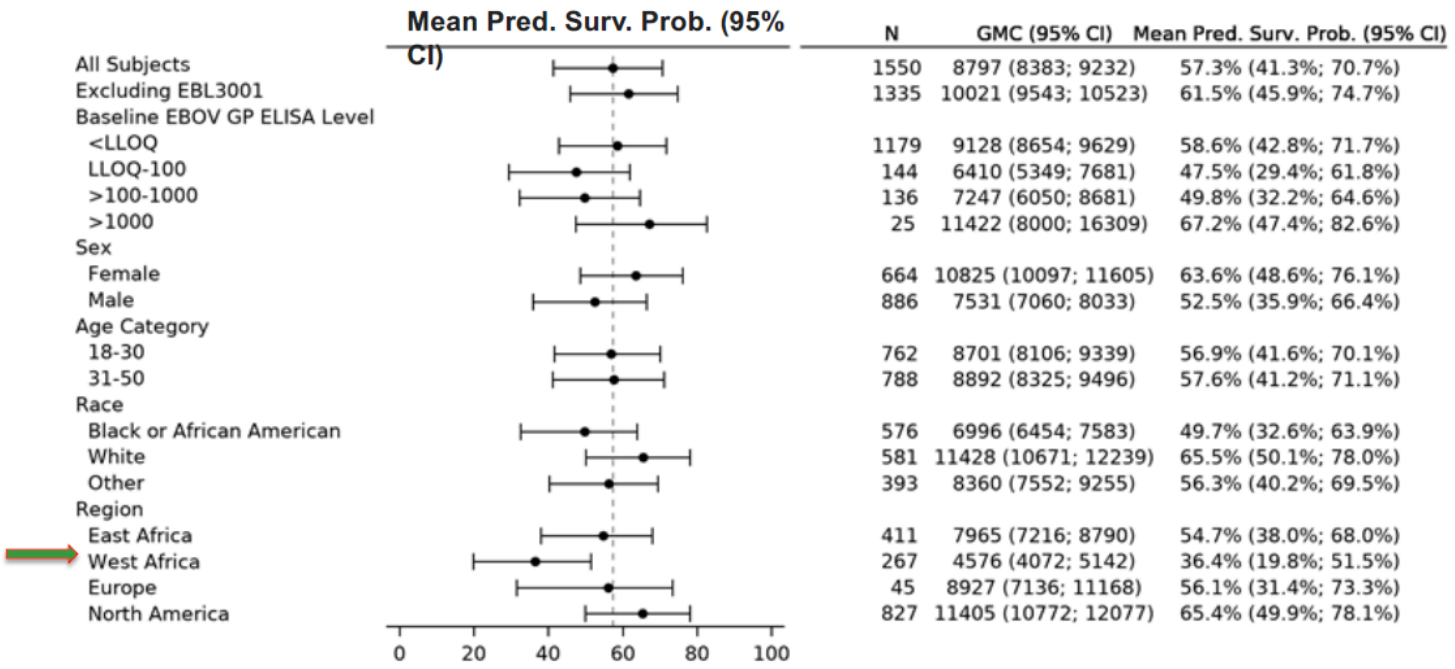
- **Evidence for clinical benefit successfully demonstrated at final analysis**
- In view of the stringency of the model, the point estimate cannot be used for absolute quantification of vaccine efficacy in humans.
- Estimate of clinical effectiveness and duration of protection to be demonstrated in subsequent studies

Interim analysis in Bockstal et al NPJ vaccines 2022

Ebola: Pre-clinical data that led to the approval of Zabdeno/Mvabea

Immuno-bridging Statistical Analysis

Final Immuno-bridging (PPS)
Subgroup analysis



	N	GMC (95% CI)	Mean Pred. Surv. Prob. (95% CI)
All Subjects	1550	8797 (8383; 9232)	57.3% (41.3%; 70.7%)
Excluding EBL3001	1335	10021 (9543; 10523)	61.5% (45.9%; 74.7%)
Baseline EBOV GP ELISA Level			
<LLOQ	1179	9128 (8654; 9629)	58.6% (42.8%; 71.7%)
LLOQ-100	144	6410 (5349; 7681)	47.5% (29.4%; 61.8%)
>100-1000	136	7247 (6050; 8681)	49.8% (32.2%; 64.6%)
>1000	25	11422 (8000; 16309)	67.2% (47.4%; 82.6%)
Sex			
Female	664	10825 (10097; 11605)	63.6% (48.6%; 76.1%)
Male	886	7531 (7060; 8033)	52.5% (35.9%; 66.4%)
Age Category			
18-30	762	8701 (8106; 9339)	56.9% (41.6%; 70.1%)
31-50	788	8892 (8325; 9496)	57.6% (41.2%; 71.1%)
Race			
Black or African American	576	6996 (6454; 7583)	49.7% (32.6%; 63.9%)
White	581	11428 (10671; 12239)	65.5% (50.1%; 78.0%)
Other	393	8360 (7552; 9255)	56.3% (40.2%; 69.5%)
Region			
East Africa	411	7965 (7216; 8790)	54.7% (38.0%; 68.0%)
West Africa	267	4576 (4072; 5142)	36.4% (19.8%; 51.5%)
Europe	45	8927 (7136; 11168)	56.1% (31.4%; 73.3%)
North America	827	11405 (10772; 12077)	65.4% (49.9%; 78.1%)

Observed clinical benefit not driven by inclusion of potentially pre-exposed Sierra Leone subjects.

- Sensitivity analyses fully consistent with primary analysis.
- Trend to lower prediction in West-Africa, influenced by lower immune responses in Sierra Leone.

East Africa: *Kenya, Uganda;* ***West Africa:*** *Sierra Leone, Burkina Faso, Cote d'Ivoire,* ***Europe:*** *France, UK;* ***North America:*** *US*

Interim analysis in Bockstal et al NPJ vaccines 2022

Effectiveness of CHIKV vaccine VLA1553 demonstrated by passive transfer of human sera

Pierre Roques,[1] Andrea Fritzer,[2] Nathalie Dereuddre-Bosquet,[1] Nina Wressnigg,[2] Romana Hochreiter,[2] Laetitia Bossevot,[1] Quentin Pascal,[1] Fabienne Guehenneux,[3] Annegret Bitzer,[2] Irena Corbic Ramljak,[2] Roger Le Grand,[1] Urban Lundberg,[2] and Andreas Meinke[2]

[1]Université Paris-Saclay, INSERM, CEA, Center for Immunology of Viral, Auto-Immune, Hematological and Bacterial diseases (IMVA-HB/IDMIT), Fontenay-aux-Roses, France. [2]Valneva Austria GmbH, Campus Vienna Biocenter 3, Vienna, Austria. [3]Valneva SE, Saint Herblain, France.

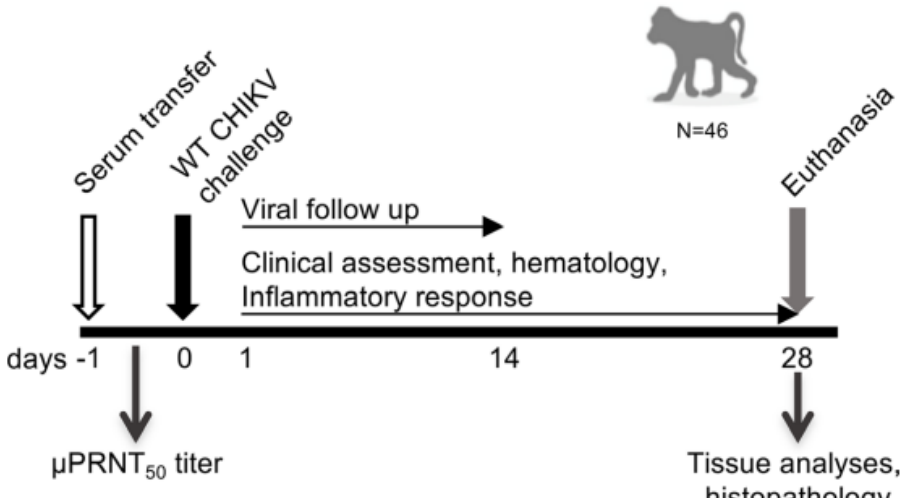


Table 2. Peak viremia for animals with different µPRNT$_{50}$ titer thresholds.

		µPRNT$_{50}$ ≥ 50 (*n* = 13)	µPRNT$_{50}$ ≥ 100 (*n*=4)	µPRNT$_{50}$ ≥ 150 (*n* = 2)
Peak viremia (copies/mL) Day 2–6	Geometric mean	941.1	16.3	10
	[95% CI]	[100, 8846]	[4, 77]	[10, 10]
Number of NHPs with detected CHIKV RNA	Not detected	4 (30.8%)	3 (75.0%)	2 (100%)
	Detected	9 (69.2%)	1 (25.0%)	0 (0.0%)

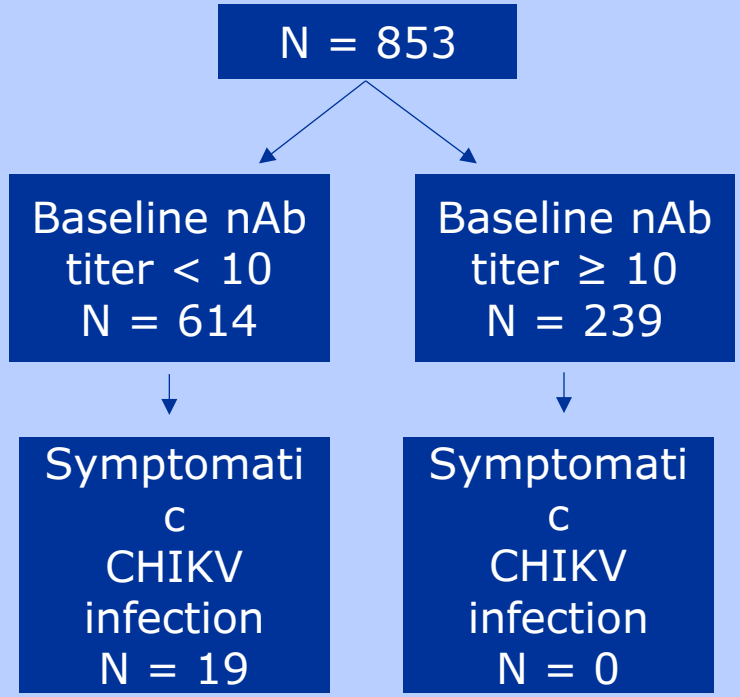
The geometric mean for the peak viremia (copies/mL) is shown for each group of animals assigned to the 3 µPRNT$_{50}$ thresholds. Numbers of animals with or without detectable CHIKV RNA were calculated for the 3 µPRNT$_{50}$ thresholds. Therefore, animals with an µPRNT ≥ 150 are included in the µPRNT$_{50}$ ≥ 100 and µPRNT$_{50}$ ≥ 50 columns, and animals with an µPRNT ≥ 100 are included in the µPRNT$_{50}$ ≥ 50 column. Peak copies/mL values reported as 0 were set to 10 for this summary.

jciinsight-7-160173.pdf (nih.gov)

Sero-epidemiological studies

Sero-epidemiology

- Prospective sero-epidemiologic study Philippines 2012-2014
- Initial publication 1st year Yoon et al. 2015
- Presence of baseline nAb strongly correlates with protection against symptomatic infection
- Assay used: PRNT80
- Longitudinal cohort: protection lasts at least 2 years (Yoon et al. 2020)



From Yoon et al, PLoS Negl Trop Dis (2015) 9(5) : e0003764; Yoon et al, IJID (2020) 95: 167–173

Real-world effectiveness of MVA-BN demonstrated

In real-world observational studies vaccine effectiveness estimates ranged:

- from 35% (95% CI, -2-59) to 89% (95% CI, 76-95) after one dose
- from 66% (95% CI, 47-78) to 90% (95% CI, 86-92) after two doses

Table 8 Vaccine effectiveness at least 14 days after vaccination[a]

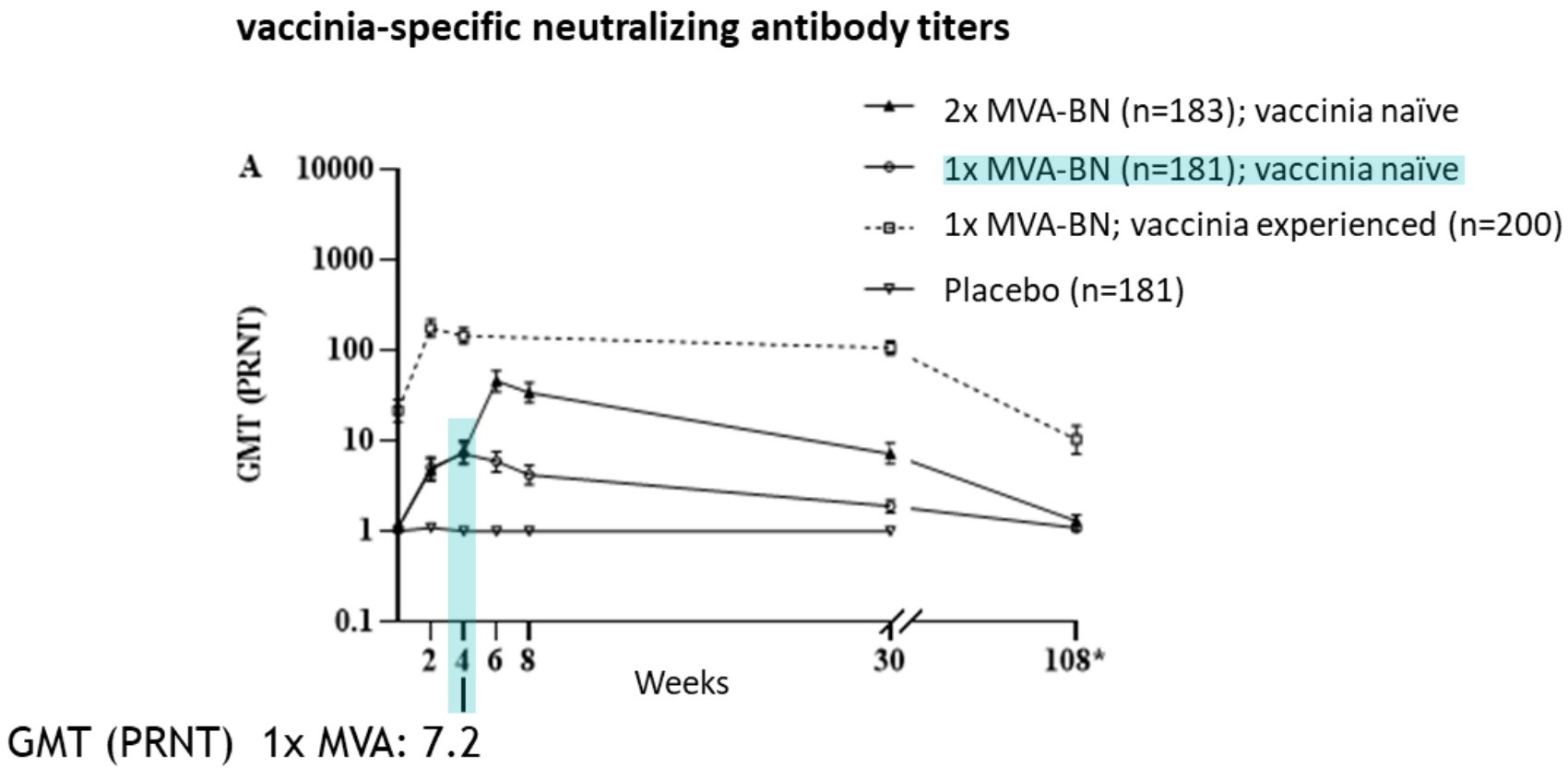
Country	Study Design, Period	Vaccination strategy	1-dose effectiveness % [95% CI]	2-dose effectiveness % [95% CI]
US	Case-control Aug 2022-Mar 2023	PrEP/PEP	77% (60-87)	89% (56-97)
	Case-control Aug 2022-Nov 2022	PrEP	36% (22-47)*	66% (47-78)*
	Retrospective cohort May 2022-Dec 2022	PrEP/PEP	81% (64-90)*	83% (28-96)*
	Case-coverage Jul 2022-Oct 2022	PrEP/PEP	86% (83-89)*	90% (86-92)*
	Case-control Jun 2022-Dec 2022	PrEP/PEP	68% (25-87)*	89% (44-98)*
Spain	Retrospective cohort Jul 2022-Dec 2022	PrEP	79% (33-100)*,**	-
	Prospective cohort May 2022-Aug 2022	PEP	89% (76-95)[a]	-
Canada	Case-control Jun 2022-Sep 2022	PrEP	35% (-2-59) 65% (1-87)***	-
UK	Case-coverage Jul 2022-Dec 2022	PrEP	78% (54-89)**	-

Note: all data are adjusted vaccine effectiveness, based on subcutaneous administration, unless indicated otherwise.
*Covers both subcutaneous and intradermal administrations.
**Crude vaccine effectiveness.
***Based on individual-level data supplemented with questionnaire responses on risk behaviour.
[a] PEP administered ≤ 14 days after exposure.

In a US surveillance study, the estimated relative risk reduction of mpox-related hospitalisation was 73% after one MVA-BN dose and 80% after two doses.

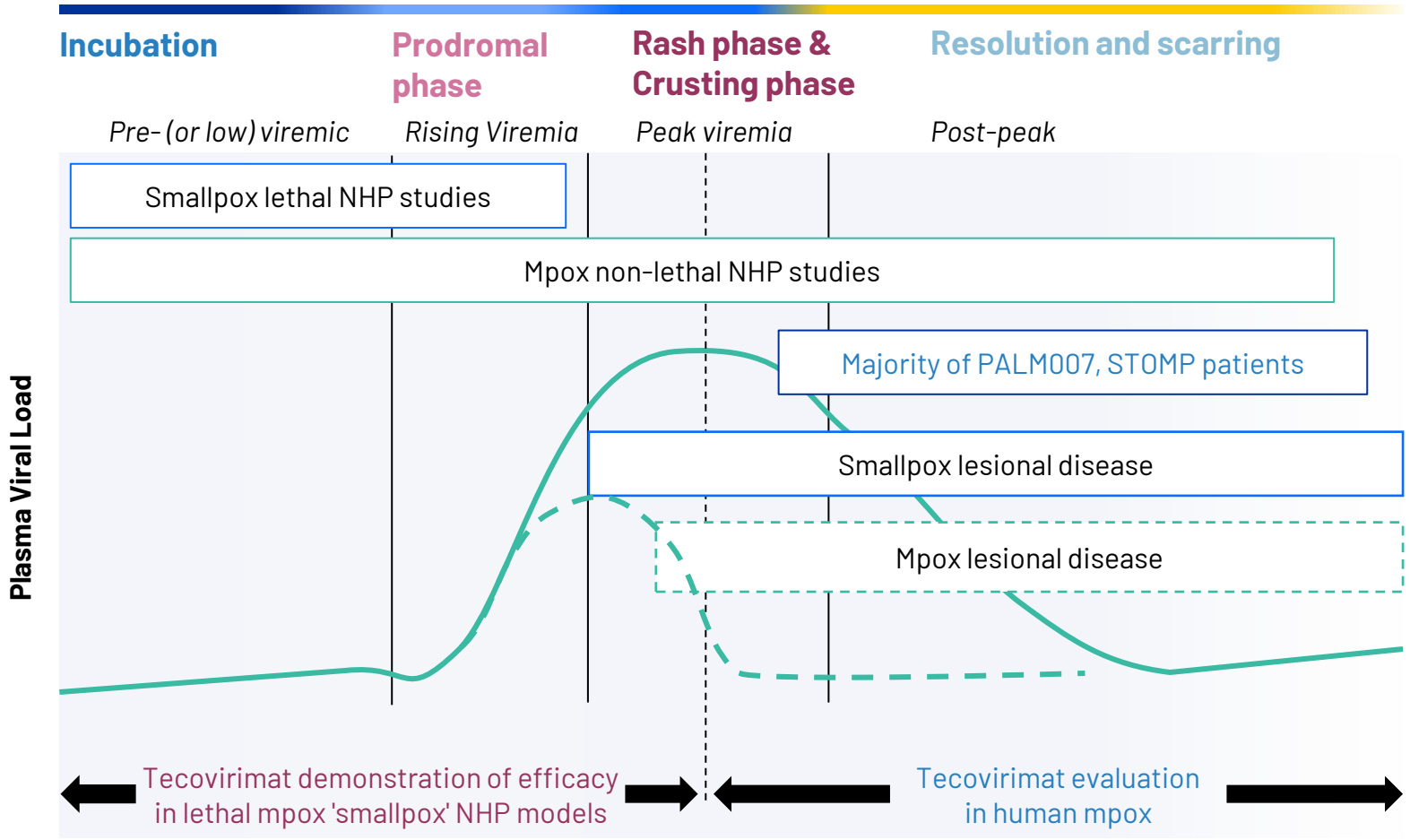
1. Imvanex SmPC. European Medicines Agency. Last updated Jan 2025. Available at: https://www.ema.europa.eu/en/documents/product-information/imvanex-epar-product-information_en.pdf.

Phase 2 trial: low vaccinia-specific neutralizing antibody titers after 1 dose of MVA-BN in vaccinia naïve subjects



Ilchmann H et al. Single and 2-dose vaccinations with MVA-BN® induce durable B cell memory responses in healthy volunteers that are comparable to older generation replicating smallpox vaccines. Randomized Controlled Trial J Infect Dis . 2023 May 12;227(10):1203-1213.

Understanding Disease Phases and Correlation with Nonclinical and Clinical Data Critical

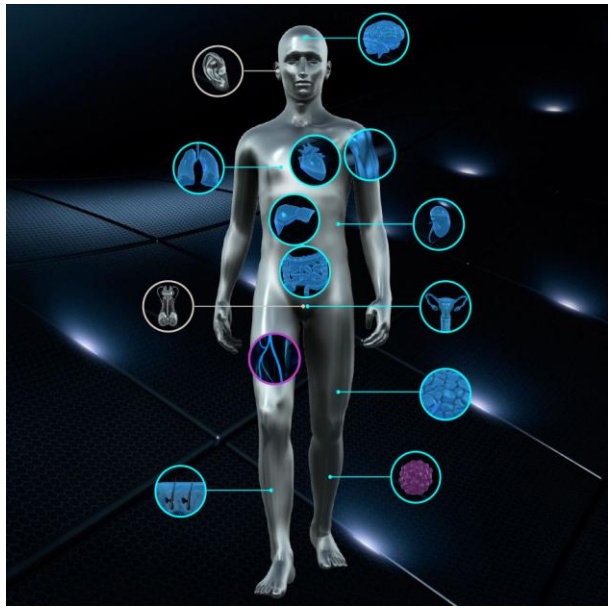


Tecovirimat developed to reduce mortality from smallpox leveraging lethal animal models

Significant clinical data has been collected on mpox (STOMP, PALM007 etc.), were patients predominantly in the post-peak viral load phase

Potential tecovirimat benefit in mpox patients; new nonclinical mpox study designed to help optimize clinical treatment paradigm in mpox patients

Why Microphysiologic Systems (MPS)?



Goal: To develop physiologic, pathophysiologic, 3D human-derived *in vitro* models, *to be used as*:

- Infectious disease models for basic research
- Product development tools to evaluate MCMs and predict activity/efficacy in humans

Rationale:

- Poor predictive quality of animal models for efficacy in humans
- Evaluate efficacy/toxicity of MCMs in relevant (human) cells/tissues
- Minimize requirement for animal-adapted pathogens and/or modified hosts
- Evaluate *host*-directed MCMs
- Identify human biomarkers of disease

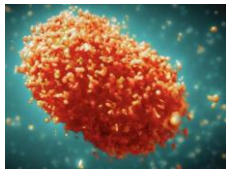
and, importantly…

- Reduced use of and reliance upon experimental animals –
- important now with critical shortage of NHPs

Terminology:
MPS *= human* ***biomimetic****, and includes* ***Organoids****,* ***Organ on a Chip****, and complex in vitro models (****CIVMs****), New Approach Methodologies (****NAMs****), etc.*

Acceptability of Sponsor's Postmarketing Plan or Approach

- There is no standardized postmarketing protocol for products approved under the Animal Rule
  - Acceptability is contextually/situationally determined for each product
- Regulatory review of the marketing application, including the postmarketing plan or approach, is conducted at the level of the product review division, with other FDA experts consulted as needed
  - In CDER, application review is based on the MCM's proposed indication



Combining design approaches to monitor mpox vaccines

SEMVAc CHARITÉ UNIVERSITÄTSMEDIZIN BERLIN TEMVAc

Multicentre (N=28) **prospective** non-interventional **cohort** study

Recruitment start: July 2022 (peak of outbreak in **Germany** in August)

Focus on **safety/reacto**

→

Retrospective cohort study using **target trial emulation** in the same centres to complement safety data and generate **effectiveness** data

+

USMVAc

Retrospective cohort study: **secondary use** of healthcare data representative of insured US population (HealthVerity)

Safety and effectiveness of MVA-BN vaccination against mpox in at-risk individuals in Germany (SEMVAc and TEMVAc): a combined prospective and retrospective cohort study

David Hillus, Ngoc Han Le, Pinkus Tober-Lau, Anne-Katrin Fietz, Christian Hoffmann, Regina Stegherr, Leu Huang, Axel Baumgarten, Florian Voit, Markus Bickel, Gal Goldstein, Christoph Wyen, Hartmut Stocker, Thomas Wünsche, Marcel Lee, Hubert Schulbin, Mathias Vallée, Ulrich Bohr, Anja Potthoff, Christiane Cordes, Caroline Isner, Bethany Knox, Antonio Carmona, Nicole Stobäus, Ran Balicer, SEMVAc Study Group*, Florian Kurth†, Leif Erik Sander†

EUPAS50093 (Lancet Infect Dis. 2025;25(7):775-787)

Article

Effectiveness and Safety of the MVA–BN Vaccine against Mpox in At-Risk Individuals in the United States (USMVAc)

Soowoo Back [1], Bethany Knox [2], Ciara Coakley [2], Nicolas Deltour [2], Emmanuelle Jacquot [2], Hanaya Raad [2] and Elizabeth M. Garry [1,*]

EUPAS104386 (Vaccines (Basel) 2024;12(6):651)

EMA

Pragmatic clinical trials using EHR – influenza vaccines

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

High-Dose Influenza Vaccine Effectiveness against Hospitalization in Older Adults

N.D. Johansen,[1,2] D. Modin,[1,2] M.M. Loiacono,[3,4] R.C. Harris,[5] M. Dufournet,[6] C.S. Larsen,[7,8] L. Larsen,[9] L. Wiese,[10] M. Dalager-Pedersen,[11,12] B.L. Claggett,[13] K.H. Janstrup,[1,2] K.V. Bartholdy,[1,2] K.F. Bernholm,[1,2] J.I.-M.H. Borchsenius,[1,2] F.S. Davidovski,[1,2] L.W. Davodian,[1,2] M. Dons,[1,2] L.S. Duus,[1,2] C. Espersen,[1,2] F.H. Fussing,[1,2] A.M.R. Jensen,[1,2] N.E. Landler,[1,2] A.C.F. [illegible] A.B. Nielsen,[1,2] C.I. Ottosen,[1,2] M. Sengeløv,[1,2] K.G. S[illegible] M.J. Landray,[14] G.H. Gislason,[1,15,16] L. Køber,[15,17] L[illegible] P. Sivapalan,[15,20] C.J.-M. Martel,[21] J.U.S. Jensen,[15,20] an[illegible]

Value of randomisation!

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

High-Dose Influenza Vaccine to Reduce Hospitalizations

J. Pardo-Seco,[1-5] C. Rodríguez-Tenreiro-Sánchez,[1-3,6,7] I. Giné-Vázquez,[1-3] N. Mallah,[1,2,8,9] S. Mirás-Carballal,[10] M. Piñeiro-Sotelo,[10] M. Cribeiro-González,[11] [illegible][12] I. Rivero-Calle,[1-3,6,7] X. Bello,[1-5] [illegible][6,7] A. Salas,[1,3-5] R.C. Harris,[13] [illegible] M. Dufournet,[17] N.D. Johansen,[18,19] [illegible][1] C. Durán-Parrondo,[10] and [illegible] for the GALFLU Trial Team*

Methodological aspects to be reviewed

Table 2. Primary and Secondary End Points and Relative Vaccine Effectiveness.*

End Point	High-Dose Vaccine (N=166,218)	Standard-Dose Vaccine (N=166,220)	Relative Vaccine Effectiveness†	P Value‡
	no. of participants (%)		%	
Primary end p[illegible]				
Hospitalizatio[illegible] pneumoni[illegible]				
Secondary en[illegible]				
Hospitalization for cardiorespiratory disease	3,735 (2.25)	3,962 (2.38)	5.7 (1.4 to 9.9)	
Hospitalization for any cause	15,585 (9.38)	15,921 (9.58)	2.1 (–0.1 to 4.3)	
Death from any cause	1,116 (0.67)	1,089 (0.66)	–2.5 (–11.6 to 5.9)	
Hospitalization for influenza§	101 (0.06)	179 (0.11)	43.6 (27.5 to 56.3)	
Hospitalization for pneumonia	1,045 (0.63)	1,050 (0.63)	0.5 (–8.6 to 8.8)	
Exploratory end point				
Hospitalization for laboratory-confirmed influenza¶	177 (0.11)	276 (0.17)	35.9 (22.2 to 47.3)	

Table 2. Primary and Other End Points.*

End Point	High-Dose Vaccine (N=67,093)	Standard-Dose Vaccine (N=66,789)	Relative Vaccine Effectiveness (95% CI)
			percent
[illegible] pneumonia or influenza			23.7 (6.6 to 37.7)
Secondary end point			
Cardiorespiratory hospitalization	985 (1.47)	1071 (1.60)	8.4 (0.1 to 16.1)
Hospitalization for any cause	4336 (6.46)	4427 (6.63)	2.5 (–1.7 to 6.5)
Death from any cause	305 (0.45)	348 (0.52)	12.8 (–2.0 to 25.4)
Hospitalization for influenza	63 (0.09)	92 (0.14)	31.8 (5.0 to 51.3)
Hospitalization for pneumonia	116 (0.17)	137 (0.21)	15.7 (–8.7 to 34.8)
Exploratory end point: laboratory-confirmed influenza hospitalization	72 (0.11)	89 (0.13)	19.5 (–11.1 to 41.8)

Conclusions

- The pathway of approval based on non-clinical models remains valid but requires case-by-case evaluation
- Ability of the model to mimic human disease and to be standardized are key factors
- Role of the the inoculation route and dose
- Definition of a protection threshold, e.g. through passive Abs transfer, or protection modelling curves have been used to approve vaccines in absence of clinical efficacy data
- For vaccines, clinical immunogenicity can be relevant based on several factors such as knowledge on correlates of protection from natural history or other vaccines that showed protection
- An entirety of the evidence approach supported
- However, differences in vaccines and pathogens with respect to mechanism of protection and other factors to be considered
- 3R principles to be followed as much as possible and innovative methods without animals encouraged
- Clinical studies to be conducted post-approval with a clear ranking from RCTs to RWE

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Thank you

marco.cavaleri@ema.europa.eu

Follow us