# *REAL-WORLD EVIDENCE TO CONFIRM VACCINE BENEFIT: MPOX VACCINE*

*Victoria Jenkins, PhD*
*Bavarian Nordic*

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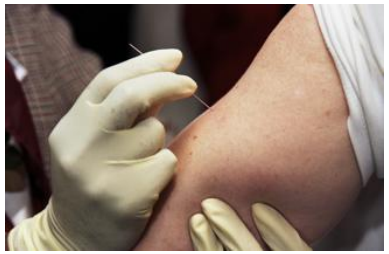
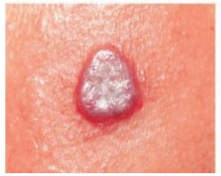
# Traditional replicating smallpox vaccines vs. MVA-BN

## Replicating smallpox vaccines[1,2]

- Replicating vaccinia virus
- Induce a „take“





## Modified Vaccinia Ankara-Bavarian Nordic (MVA-BN)

- Attenuated vaccinia virus
- Non-replicating in human cells

1. https://www.cdc.gov/smallpox/clinicians/vaccination-administration2.html 2. ACAM2000 prescribing information

# Regulatory approval timeline of MVA-BN

**2013**

IMVANEX approved under exceptional circumstances for active immunisation against **smallpox** in adults

**2019**

JYNNEOS approved for prevention of smallpox and monkeypox disease in adults 18 years of age and older determined to be at high risk for **smallpox or monkeypox** infection

**2022**

Expansion of approval:

Active immunisation against **smallpox, monkeypox and disease caused by vaccinia virus** in adults

**2013**

IMVAMUNE approved for active immunization against **smallpox** infection and disease in adults who have a contraindication to 1st or 2nd generation smallpox vaccines*

**2020**

Expansion of approval:

Active immunization against **smallpox, monkeypox and related orthopoxvirus infection** and disease in adults 18 years of age and older determined to be at high risk for exposure

* based on limited clinical testing in humans under the provision of the Extraordinary Use New Drug regulations

JYNNEOS/Imvanex/Imvamune prescribing information

# Overview of pre-clinical data with MVA

- Across 7 non-human primate (NHP) monkeypox challenge studies, 80-100% of MVA-BN-vaccinated animals survived compared to 0-40% of control animals [1]

- In a NHP monkeypox model, comparing vaccination with 1 dose of MVA vs. 1 dose of Dryvax: [2]

  - MVA induced a faster immune response
  - MVA provided earlier protection (4/4 animals surviving vs 1/4 animals when challenged on day 4)


1. JYNNEOS prescribing information
2. Earl PL et al. Rapid protection in a monkeypox model by a single injection of a replication-deficient vaccinia virus. Proc Natl Acad Sci U S A 2008 Aug 5;105(31):10889-94.

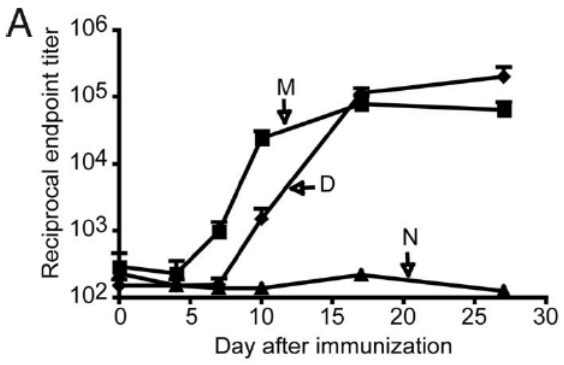
# Rapid protection in a monkeypox model by a single injection of a replication-deficient vaccinia virus

Patricia L. Earl*, Jeffrey L. Americo*, Linda S. Wyatt*, Ondraya Espenshade†, Jocelyn Bassler†, Kathy Gong†, Shuling Lin†, Elizabeth Peters†, Lowrey Rhodes, Jr.†, Yvette Edghill Spano†, Peter M. Silvera†, and Bernard Moss*‡

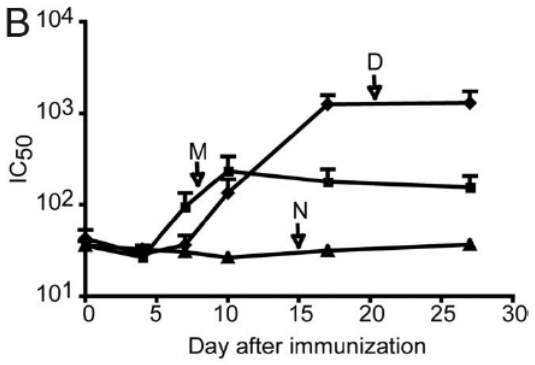
*Laboratory of Viral Diseases, National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, MD 20892-3210; and †Southern Research Institute, Frederick, MD 21701

- To study immunogenicity, macaques received 1 dose of MVA (n=4) i.m. or 1 dose Dryvax (n=4) by skin scratch
- Vaccinia virus-specific IgG, neutralizing antibodies, CD8+ T cells were detected earlier for MVA than for Dryvax

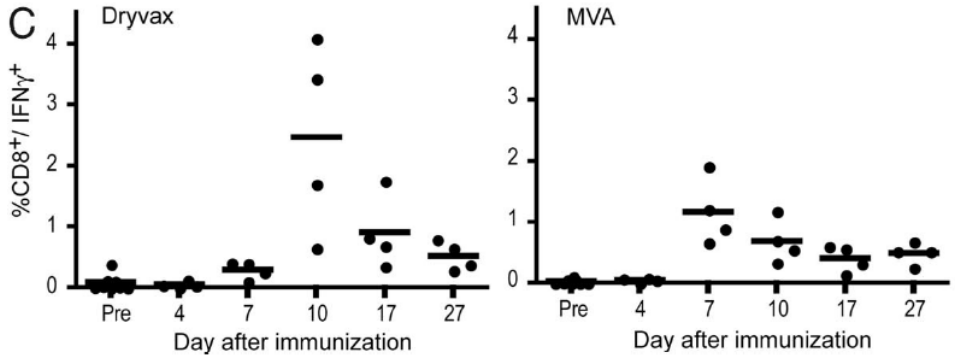
Anti-vaccinia virus IgG titers (ELISA )




Neutralizing antibody titers

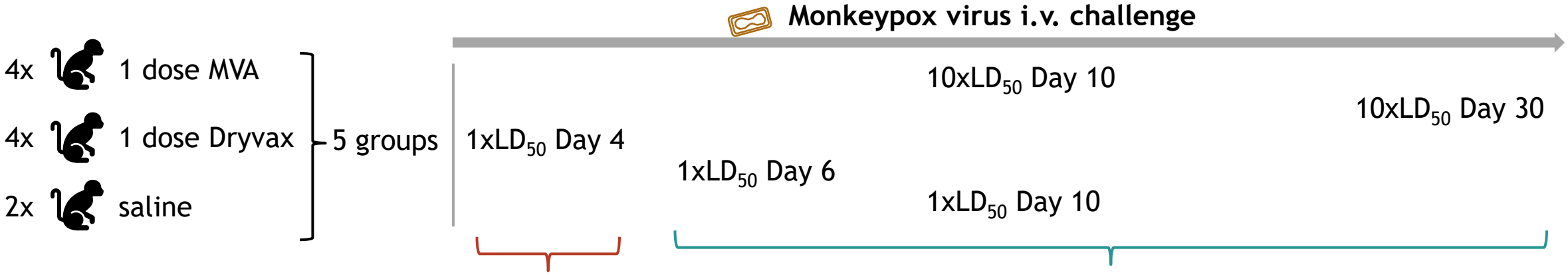



Vaccinia virus-specific CD8+ T cell cells

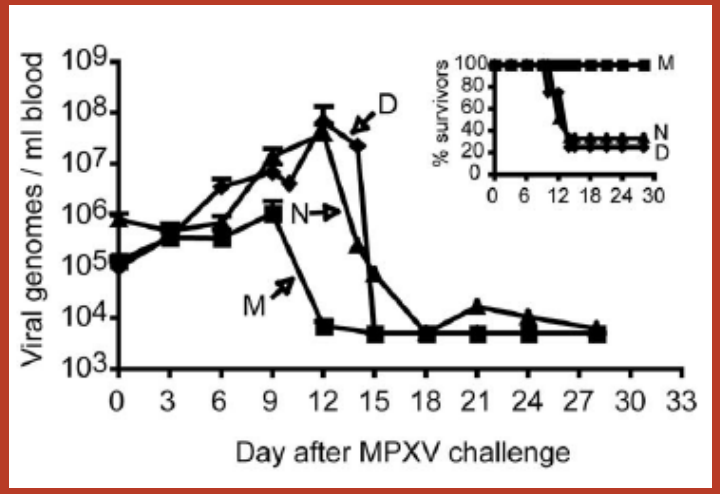



M = MVA D = Dryvax N = not vaccinated

Earl PL et al. Rapid protection in a monkeypox model by a single injection of a replication-deficient vaccinia virus. Proc Natl Acad Sci U S A 2008 Aug 5;105(31):10889-94.




- MVA group: 4 of 4 animals survived
- Dryvax group: 1 of 4 animals survived




- Viral loads and number of skin lesions generally higher in the MVA group
- Animals were clinically protected (except for 1 animal in the MVA group)

M = MVA D = Dryvax N = not vaccinated

Earl PL et al. Rapid protection in a monkeypox model by a single injection of a replication-deficient vaccinia virus. Proc Natl Acad Sci U S A 2008 Aug 5;105(31):10889-94.

# MVA-BN has been investigated in close to 9,000 individuals across more than 20 clinical trials (1/2)

## 2001–2006[a,b]

**Phase I** study in healthy subjects (N = 86)[1,2]

**Phase II** dose-finding study (N = 164)[3,4]

**Phase I** study in subjects with atopic dermatitis (N = 60)[5,6]

**Phase I** study evaluating different MVA-BN dose regimens followed by administration of Dryvax (N = 75)[7,8]

**Phase I** study in subjects with HIV (N = 151)[9,10]

**Phase II** study evaluating 1 vs 2 doses in pre-immune versus vaccinia-naïve subjects, respectively (N = 564)[11,12]

**Phase II** study in pre-immune vs vaccinia-naïve subjects with HIV (N = 579)[13,14]

**Phase II** study in subjects with atopic dermatitis (N = 632)[15,16]

## 2007–2008[a,b]

**Phase I/II** study evaluating different vaccination regimens in vaccinia-naïve adults (N = 191)[17,18]

**Phase II** 2-year booster study (N = 152)[12,19]

**Phase I** study in haematopoietic stem cell transplant subjects (N = 20)[20,21]

[a] Date ranges reflect study start dates. [b] Participant numbers reflect all individuals who received an MVA-BN vaccine dose.
Please see slide notes for a list of abbreviations and references.

# MVA-BN has been investigated in close to 9,000 individuals across more than 20 clinical trials (2/2)

## 2009–2013[a,b]

**Phase II** study to evaluate 1 and 2 doses in 56–80-year-old vaccinia-experienced subjects (N = 120)[1,2]

**Phase II** study evaluating a high dose in vaccinia-naïve subjects (N = 91)[3,4]

**Phase II** study evaluating subcutaneous/intradermal administration of liquid vaccine versus subcutaneous administration of lyophilised vaccine (N = 524)[5,6]

**Phase III** liquid-frozen MVA-BN lot consistency study (N = 3,003)[7,8]

**Phase II** study to compare liquid-frozen and freeze-dried MVA-BN (N = 651)[9]

**Phase II** study of different immunisation schedules and delivery systems in vaccinia-naïve adults (N = 435)[10,11]

## 2014 and beyond[a,b]

**Phase II** study to assess the safety and immunogenicity in immunocompromised subjects with HIV infection (N = 87)[12,13]

**Phase III** study to compare MVA-BN to ACAM2000 (N = 220)[14,15]

**Phase III** freeze-dried MVA-BN lot consistency study (N = 1,129)[16,17]

**Phase II** study evaluating the immunogenicity and safety of MVA-BN in adolescents and adults (N = 450)[18]

Immunogenicity and Safety Study of MVA-BN Vaccine in Children From 2 Years to <12 Years (NCT06549530)

[a] Date ranges reflect study start dates. [b] Participant numbers reflect all individuals who received an MVA-BN vaccine dose.
Please see slide notes for a list of abbreviations and references.

# *WHY REAL-WORLD EVIDENCE (RWE) FOR MPOX VACCINES IS ESSENTIAL*

# Why Real-World Evidence (RWE) for Mpox Vaccines Is Essential

- **Licensure of MVA-BN was based on immunogenicity & animal challenge, not direct mpox efficacy**
    - Initial approvals of MVA-BN relied on orthopox animal-challenge models and comparative immunogenicity vs replicating smallpox vaccines because smallpox is eradicated and mpox efficacy data were not yet available


Imvanex SmPC, EMA, last updated Jan 2025 (includes mpox indication and RWE VE ranges).
EMA. Imvanex EPAR – Public Assessment Report, 2013 (approval under exceptional circumstances based on non-clinical and immunogenicity data).
Duffy J et al. *MMWR* 2022;71:1555–1559. Safety Monitoring of JYNNEOS Vaccine During the 2022 Mpox Outbreak ‘ United States, May 22–October 21, 2022.
Mason LMK et al. *Vaccine* 2024. “MVA-BN vaccine effectiveness: a systematic review of real-world evidence in outbreak settings.”
Back S et al. *Vaccines* 2024;12(6):651. Effectiveness and Safety of the MVA–BN Vaccine against Mpox Disease.
Bavarian Nordic press release, 26 July 2024. Positive CHMP opinion to include mpox real-world effectiveness data (VE up to ~90% after 2 doses).

# Why Real-World Evidence (RWE) for Mpox Vaccines Is Essential

- **RWE evaluates performance in real high-risk and special populations**
    - Post-licensure data capture vaccine impact in groups under-represented in trials (e.g. people with HIV, dermatologic disease, other immunocompromised conditions, etc.) across heterogeneous exposure networks and health systems.

- **RWE is critical for ongoing benefit-risk and long-term protection assessment**
    - Large-scale safety surveillance has not identified unexpected safety concerns, while emerging immunogenicity studies suggest waning antibodies and highlight the need for RWE on **durability, boosters**


Imvanex SmPC, EMA, last updated Jan 2025 (includes mpox indication and RWE VE ranges).
EMA. Imvanex EPAR – Public Assessment Report, 2013 (approval under exceptional circumstances based on non-clinical and immunogenicity data).
Mason LMK et al. *Vaccine* 2024. "MVA-BN vaccine effectiveness: a systematic review of real-world evidence in outbreak settings."
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Duffy J et al. *Sex Transm Dis* 2024. JYNNEOS vaccine safety surveillance using VAERS and v-safe, United States 2022–2023.
Grabenstein JD et al. *Expert Rev Vaccines* 2024. Vaccines against mpox: MVA-BN and LC16m8 (review of human, animal and RWE data).
Oom AL et al. *J Virol* 2025. The two-dose MVA-BN mpox vaccine induces a non-durable and low-avidity MPXV-specific antibody response.
Adamu AA et al. *Hum Resour Health* 2025. Appraising the current landscape of reviews on mpox (identifies gaps in MVA-BN effectiveness and immunogenicity data, especially in African settings).

# Real-world safety surveillance was conducted during a period in which ~1 million MVA-BN doses were administered in the US

The CDC **monitors MVA-BN vaccine safety** using:

- The **Vaccine Adverse Event Reporting System**
- The **Vaccine Safety Datalink**
- **Single-patient emergency Investigational New Drug** procedures

  For persons aged <18 years who were vaccinated before 9 August 2022

During the **surveillance period** (22 May to 21 October 2022):

- **987,294 MVA-BN doses** were administered (**66% first** and **34% second** doses)
- **90%** of vaccinated persons were **male**
- **51%** were administered **intradermally**, **34% subcutaneously**, and **15%** by **unknown/other** routes
- MVA-BN was administered to **1,003** persons aged **< 18 years**

CDC, Centers for Disease Control and Prevention; MVA-BN, modified vaccinia Ankara - Bavarian Nordic; US, United States.

Duffy J, et al. MMWR Morb Mortal Wkly Rep. 2022; 71:1555–1559.

# Good safety profile of MVA-BN confirmed in real-world use

- The vaccine safety profile was consistent with prelicensure studies
- The most common adverse health events reported were nonserious and included injection site reactions.
- Serious adverse events were rare among adults, and no serious adverse events have been identified among persons aged <18 years

**TABLE 2. Reporting rates for the 10 most frequently reported adverse health events* after JYNNEOS vaccine receipt, by route of administration† — Vaccine Adverse Event Reporting System, United States, May 22–October 21, 2022**

| Route of administration/ Health event | No. of reports | Reporting rate§ (95% CI) |
|---|---|---|
| **Intradermal (n = 325)** | | |
| Injection site erythema | 75 | 150 (118–188) |
| Dizziness | 66 | 132 (102–168) |
| Urticaria | 60 | 120 (91–154) |
| Injection site swelling | 51 | 102 (76–134) |
| Syncope | 43 | 86 (62–116) |
| Erythema | 42 | 84 (60–113) |
| Loss of consciousness | 41 | 82 (59–111) |
| Injection site pruritus | 40 | 80 (57–109) |
| Hyperhidrosis | 38 | 76 (54–104) |
| Pruritus | 33 | 66 (45–92) |
| **Subcutaneous (n = 212)** | | |
| Injection site erythema | 36 | 107 (75–148) |
| Injection site swelling | 36 | 107 (75–148) |
| Injection site pain | 34 | 101 (70–141) |
| Pain | 29 | 86 (57–123) |
| Erythema | 28 | 83 (55–120) |
| Dizziness | 27 | 80 (53–116) |
| Headache | 26 | 77 (50–113) |
| Fatigue | 25 | 74 (48–109) |
| Injection site pruritus | 23 | 68 (43–102) |
| Pyrexia | 23 | 68 (43–102) |

* Excluding vaccination errors and deviations from recommendations.
† Licensed and authorized routes of administration only.
§ Reports per million doses administered; total number of intradermal doses administered = 501,228 and subcutaneous doses administered = 337,950.

*Duffy J, Marquez P, Moro P, et al. Safety Monitoring of JYNNEOS Vaccine During the 2022 Mpox Outbreak — United States, May 22-October 21, 2022. MMWR Morb Mortal Wkly Rep 2022;71:1555-1559. DOI: http://dx.doi.org/10.15585/mmwr.mm7149a4.*

# MVA-BN confirmed in real-world use

| Country | Important results | Link to reference |
|---|---|---|
| United States (multi-jurisdiction) | Adjusted VE 75% (1 dose) and 86% (2 doses); protection regardless of route (SC/ID) and immunocompromise; case-control. | MMWR, 2023 (Dalton et al.) https://www.cdc.gov/mmwr/volumes/72/wr/mm7220a3.htm |
| United States (national analysis) | Two-dose series provided better protection than one dose; surveillance + immunization data linkage. | NEJM, 2023 (Deputy et al.) https://www.nejm.org/doi/full/10.1056/NEJMoa2215201 |
| United States (New York State) | 1 or 2 doses effective; >88% VE for 2 doses; case-control among diagnosed cases. | MMWR, 2023 (Rosenberg et al.) https://www.cdc.gov/mmwr/volumes/72/wr/mm7220a4.htm |
| United States (breakthroughs & severity) | <1% of fully vaccinated had breakthrough infection (May 2022–May 2024); milder illness vs unvaccinated. | MMWR, 2024 (Guagliardo et al.) https://www.cdc.gov/mmwr/volumes/73/wr/mm7320a3.htm |
| United States (hospitalization in PLHIV) | Among mpox patients with HIV, 1 Jynneos dose associated with ~72% lower odds of hospitalization (OR ≈ 0.28) vs unvaccinated; surveillance case-control. | Clinical Infectious Diseases, 2023 (Schildhauer et al.) https://pubmed.ncbi.nlm.nih.gov/37676838/ |

# MVA-BN confirmed in real-world use

| Country | Important results | Link to reference |
|---|---|---|
| **Israel** | Single-dose **VE 86%** (95% CI 59–95) against infection ≥14 days post-SC dose; retrospective cohort in at-risk men. | Nature Medicine, 2023 (Wolff Sagy et al.) https://www.nature.com/articles/s41591-023-02229-3 |
| **United Kingdom** | Single-dose **VE 78%** (95% CI 54–89) ≥14 days; UKHSA case-coverage among GBMSM at risk. | Lancet Infect Dis, 2023 (Bertran et al.) https://www.thelancet.com/journals/laninf/article/PIIS1473-3099%2823%2900057-9/fulltext |
| **England** | Single-dose **VE 58%** (95% CI 31–75) vs lab-confirmed infection; matched cohort. | BMJ, 2024 (Navarro et al.) https://www.bmj.com/content/386/bmj-2023-078243 |
| **England (2023 outcomes)** | **No vaccinated persons hospitalized** for mpox in 2023 in this analysis; epidemiologic study. | Emerging Infectious Diseases, 2024 https://wwwnc.cdc.gov/eid/article/30/10/24-0292_article |
| **Canada (Québec)** | Single dose reduced risk by ~**one-third** with admin data; **~two-thirds** after adjusting for self-reported risk factors; observational. | Clinical Infectious Diseases, 2024 (Brousseau et al.) https://academic.oup.com/cid/article/78/2/461/7285391 |
| **Spain (Madrid)** | **Post-exposure** vaccination (PEP) **adjusted VE 88.8%**; cohort during early outbreak. | Eurosurveillance, 2023 (Morales et al.) https://pmc.ncbi.nlm.nih.gov/articles/PMC10318941/ |
| **Germany (Berlin)** | One-dose protection overall (**VE 57.8%**); **84.1%** in persons **without HIV**, **34.9%** in **PLHIV**; combined prospective/retrospective cohorts (SEMVAc/TEMVAc). | Lancet Infect Dis, 2025 (Hillus et al.) https://www.thelancet.com/journals/laninf/article/PIIS1473-3099%2825%2900018-0/fulltext |

# 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)** | - |

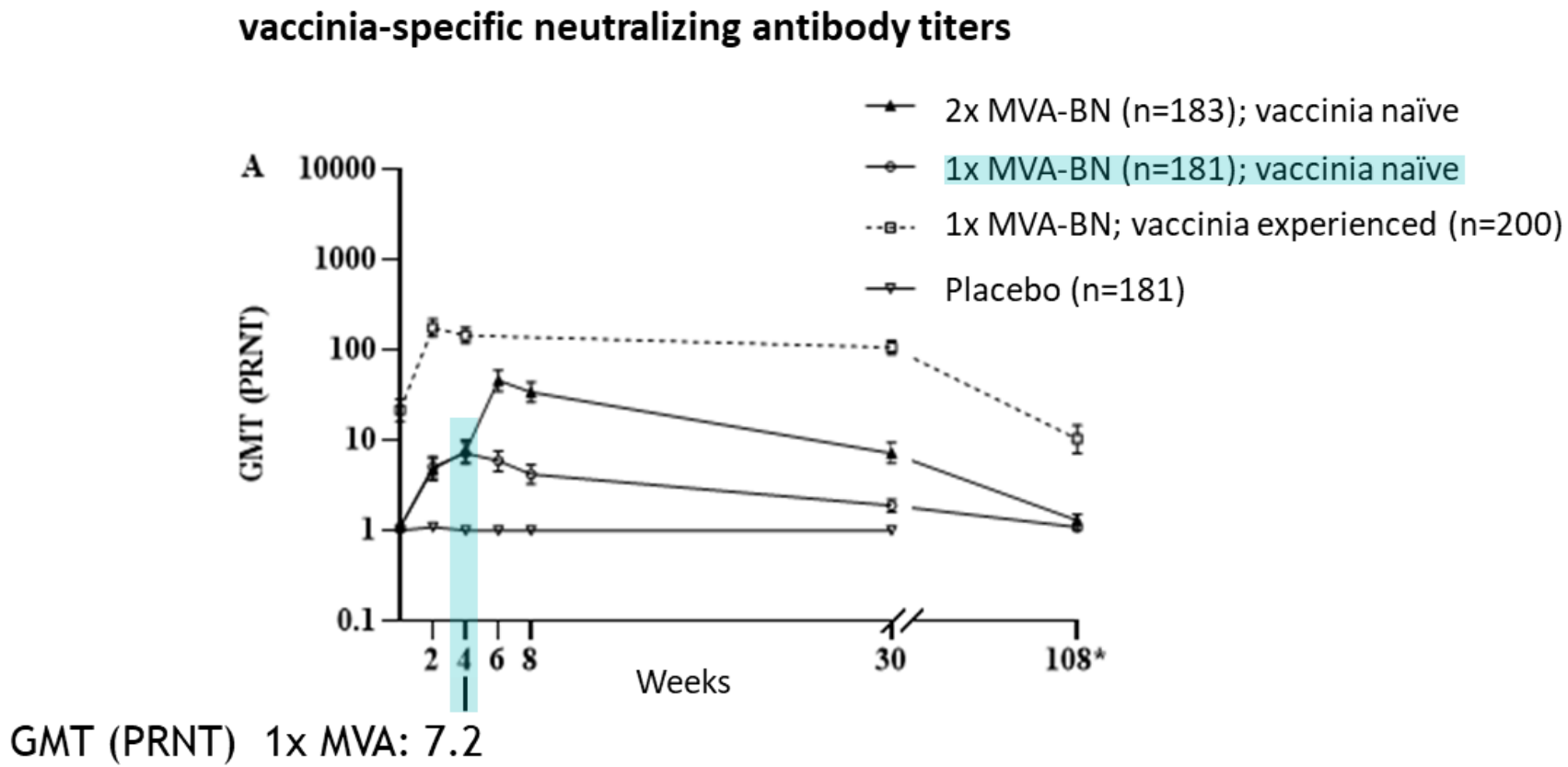
Note: all data are adjusted vaccine effectiveness, based on subcutaneous administration, unless indicated otherwise.
*Covers both subcutaneous and intradermal administrations.
**Crude vaccine effectiveness.
***Based on individual-level data supplemented with questionnaire responses on risk behaviour.
[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.*

# *WHY IMMUNE CORRELATES FOR MPOX ARE CHALLENGING*

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

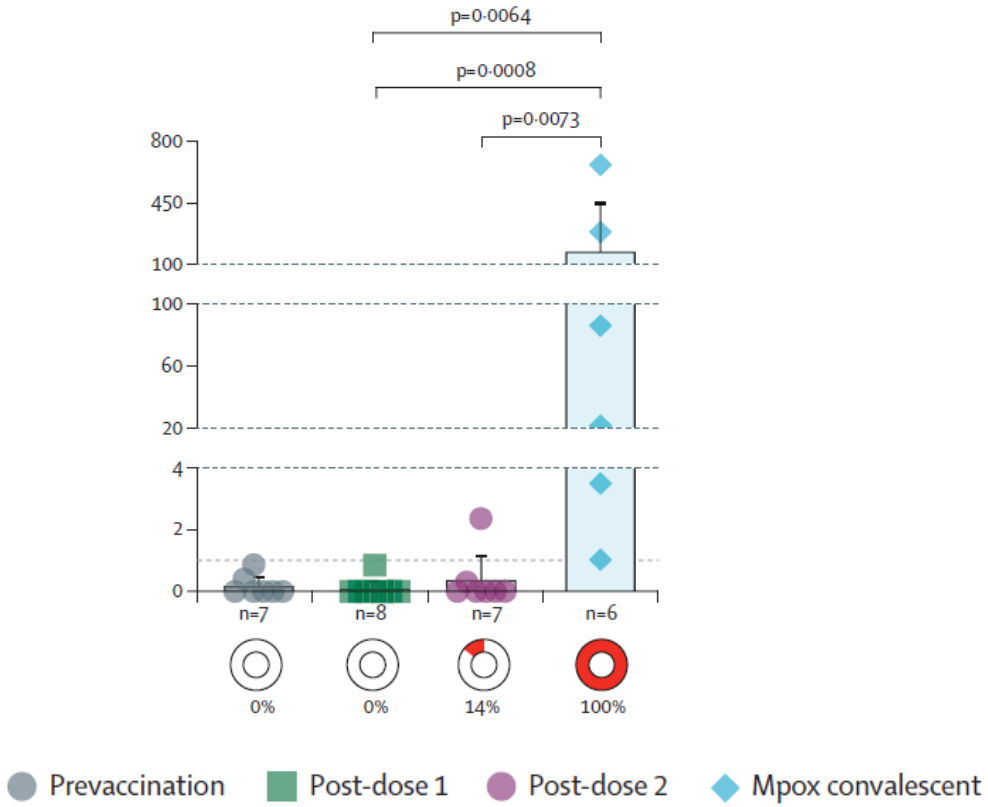



*Ilchmann H et al. Single and 2-dose vaccinations with MVA-BN® induce durable B cell memory responses in healthy volunteers that are comparable to older generation replicating smallpox vaccines. Randomized Controlled Trial J Infect Dis . 2023 May 12;227(10):1203-1213.*

# Low monkeypox virus (MPXV)-specific humoral response to 1 dose of MVA-BN

1 dose of MVA-BN induced low MPXV-specific IgG[1,2] and low MPXV-specific neutralizing titers[3,4]

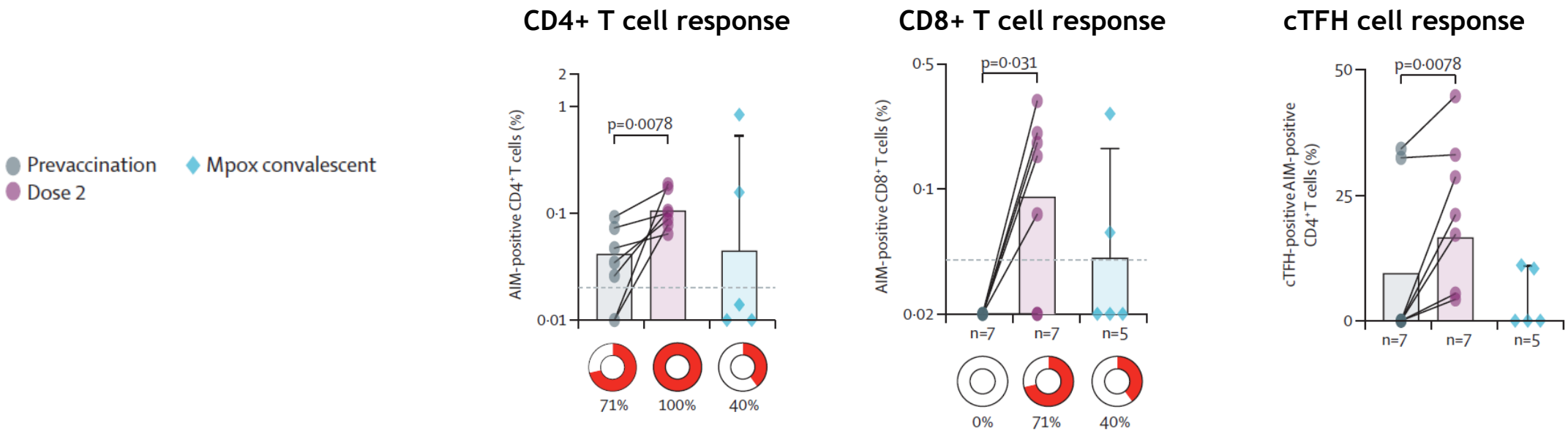
**IgG responses to a lysate from MPXV-infected cells[1]**




1. Cohn H et al. Lancet Infect Dis. 2023 Jul 17:S1473-3099(23)00352-3. doi: 10.1016/S1473-3099(23)00352-3. 2. Otter AD et al. Nat Commun. 2023 Sep 23;14(1):5948. doi: 10.1038/s41467-023-41587-x. 3. Zaeck LM et al. Nat Med. 2023 Jan;29(1):270-278. 4. Sammartino JC et al. J Med Virol 2023 May;95(5):e28778. doi: 10.1002/jmv.28778.

# MVA-BN elicited robust T-cell responses

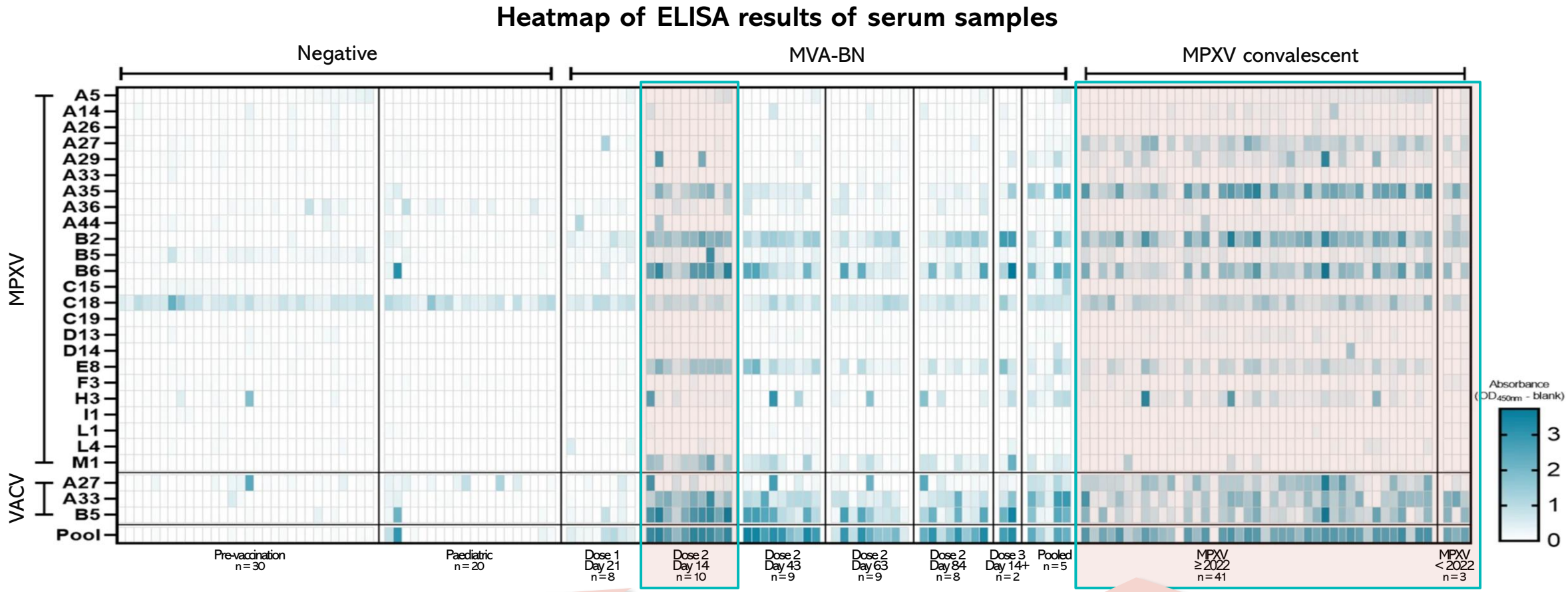
- Robust CD4+ and CD8+ T cell responses against orthopox peptides comparable to those observed after mpox infection
- Circulating T follicular helper (cTFH) cell levels significantly increased post vaccination but not post mpox infection






Cohn H et al., Mpox vaccine and infection-driven human immune signatures: an immunological analysis of an observational study. Lancet Infect Dis. 2023 Jul 17:S1473-3099(23)00352-3. doi: 10.1016/S1473-3099(23)00352-3.

# 2 doses of MVA-BN induced antibodies binding to diverse poxvirus antigens




Individuals who received 2 doses of MVA-BN (14 days post-vaccination) demonstrated diverse recognition of MPXV and VACV antigens

Response from individuals with prior MPXV infection was similar to those who were vaccinated

Otter AD, et al. Nat Commun. 2023; 14:5948.

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# Summary

- Licensure of MVA-BN was based on preclinical efficacy data and clinical trials demonstrating comparative immunogenicity vs. replicating smallpox vaccines
- Real-world effectiveness against mpox disease high after 1 dose and even higher after 2 doses
- A correlate of protection from mpox disease has not yet been defined
- Protection seems not to correlate with neutralising antibody response but might be mediated by a highly functional humoral and cellular immunity to a broad array of antigens
- RWE is essential for understanding effectiveness across populations, settings, and time